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(54) Title: INTERACTION OF ALPHA–CONOTOXIN PEPTIDES WITH NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS

(57) Abstract

This invention relates to derivatives of the conopeptide MII, an α–4/7 conotoxin peptide, in which amino acid residues are substituted as described herein while maintaining the basic activity of MII. The present invention also relates to the discovery of the 3–dimensional structure of MII, and the relationship of its structure to its specificity to the $\alpha 3\beta 2$ subtype of the neuronal nicotinic acetylcholine receptor (nAChR). The present invention also relates to computer based programs for the expression of the three–dimensional structure of MII and peptide analogs, peptide mimetics or non–peptide mimetics thereof. The structural characteristics may be correlated with biological activity to enable the design of α–4/7 conotoxin peptide analogs and peptide mimetics which demonstrate the same specificity to neuronal nAChR. Such analogs and peptide mimetics are useful as cardiovascular agents and for treating or detecting small–cell lung carcinoma (SCLC).

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TITLE OF THE INVENTION

INTERACTION OF ALPHA-CONOTOXIN PEPTIDES WITH NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS

This invention was made with Government support under Grant Nos. GM-54710, P01 48677 and MH-53631 awarded by the National Institutes of Health, Bethesda, Maryland. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The present invention relates to derivatives of the alpha conopeptide MII, an α-4/7 conotoxin peptide, in which amino acid residues are substituted as described herein while maintaining activity substantially similar to MII.

The present invention is further directed to the discovery of the 3-dimensional structure of MII and the relationship of its structure to its specificity for the α3β2 subtype of the neuronal nicotinic acetylcholine receptor (nAChR). The discovery of the 3-dimensional structure enables the design of α-4/7 conotoxin peptide analogs and peptide mimetics which will demonstrate the same specificity to neuronal nAChR. Such analogs and peptide mimetics are useful as cardiovascular agents and for treating or detecting small-cell lung carcinoma (SCLC). The present invention also relates to computer based programs for the expression of the three-dimensional structure of MII and peptide analogs, peptide mimetics or non-peptide mimetics thereof.

The publications and other materials used herein to illuminate the background of the invention and, in particular cases, to provide additional details respecting the practice, are incorporated by reference, and for convenience are numerically referenced in the following text and respectively grouped in the appended bibliography.

The α-conopeptide MII has the amino acid sequence: Gly-Cys-Cys-Ser-Asn-Pro-Val-Cys-His-Leu-Glu-His-Ser-Asn-Leu-Cys (SEQ ID NO:1). This peptide contains two disulfide bonds between the first and third cysteine residues and between the second and fourth cysteine residues. The C-terminal end may contain a carboxyl or amide group, preferably an amide group. The amino

acid at position 6 may be proline or 4-trans-hydroxyproline, preferably proline. The identification of MII is described in U.S. Patent No. 5,514,774, incorporated herein by reference.

A major challenge for neurobiology is to define the function of the multiple forms of nicotinic receptors and ion channels that have recently been discovered in the nervous system by molecular techniques. The use of gene knock-out organisms is one method for examining such function. A complementary approach is to use ligands that specifically inhibit a particular molecular form of receptor or ion channel. Such ligands must be able to discriminate between closely related members of receptor families.

Nicotinic acetylcholine receptors (nAChR) are ligand-gated ion channels which are key components of nervous systems. The classical role of these receptors was defined at the neuromuscular junction, nicotinic receptors concentrated on the muscle end plate serve as the key macromolecule that detects release of neurotransmitter from the presynaptic terminus of the motor axon. However, in addition to these skeletal muscle nicotinic receptors, many other molecular forms of nicotinic receptors exist; these are generally referred to as neuronal nicotinic receptors. In the central nervous system (CNS), nAChRs play a prominent role in modulating the release of neurotransmitters including dopamine, norepinephrine, acetylcholine, GABA and glutamate.

The small peptide toxins (conotoxins) from the venom of fish-hunting cone snail, *Conus magus*, are a natural source of ligands that discriminate between closely related molecular forms of a single receptor or ion channel family. Alpha conopeptide MII is a small peptide with selective action on neuronal nicotinic receptors. In the autonomic nervous system, MII was recently used to help pharmacologically dissect the nAChRs which mediate synaptic transmission in the parasympathetic ciliary ganglion. In frog sympathetic ganglia, MII discriminates between nAChRs in B versus C neurons. In the CNS, the specificity of MII enables identification of subunits of nAChRs which modulate nicotine-stimulated dopamine release. In retina, MII's selective block was used to confirm the role of nAChRs in the development of visual circuitry. The use of MII for detecting the presence and location of small-cell lung carcinoma (SCLC) tumors, treating a patient having SCLC and inhibiting proliferation of SCLC tumors is described in U.S. Patent 5,595,972, incorporated herein by reference. The use of MII for treating disorders resulting from nicotine stimulated dopamine release is described in U.S. Patent 5,780,433, incorporated herein by reference. The use of MII as a cardiovascular agent is described in copending provisional application Serial No. 60/031,141, filed 18 November 1996, incorporated herein by reference. To date, there have been no reports of the three-dimensional structure of MII and no systematic studies of the relationship of

the three-dimensional structure and function of the molecule, studies which are essential to the systematic design of MII analogs and mimetics.

It is desired to identify derivatives of MII, peptide analogs and peptide mimetics of α-conotoxins, generally, which are selective for specific subtypes of nAChRs and which have the uses described herein.

SUMMARY OF THE INVENTION

The present invention relates to derivatives of the alpha conopeptide MII, an α-4/7 conotoxin peptide, in which amino acid residues are substituted as described herein while maintaining activity substantially similar to MII. More specifically, the present invention is directed to the derivatives having the general formula (SEQ ID NO:2):

Xaa-Cys-Cys-Xaa-Xaa$_1$-Xaa$_2$-Xaa-Cys-Xaa$_3$-Xaa-Xaa$_4$-Xaa$_5$-Xaa-Xaa-Xaa-Cys,

wherein Xaa represents an amino acid selected from the group consisting of natural, modified or non-natural amino acids. The modifications may be by addition substitution or deletion of one or more amino acid residues. The modification may also include the addition or substitution of analogs of the amino acid themselves, such as peptidomimetics, or amino acids with altered side groups, or mimetics, e.g., organic molecules with similar space/structure/function relationships. Individual residue Xaa$_1$ is any amino acid, preferably Asn or His; Xaa$_2$ is any amino acid, preferably Pro or hydroxy-Pro; Xaa$_3$ is any amino acid, preferably His or Asn; Xaa$_4$ is any amino acid, preferably Glu; and Xaa$_5$ is any amino acid, preferably His or Asn. It is most preferred that Xaa$_1$ is Asn; Xaa$_2$ is Pro or hydroxy-Pro; and Xaa$_5$ is His. The C-terminal end may contain a carboxyl or amide group, preferably an amide group.

A second aspect of the present invention is directed to the discovery of the 3-dimensional structure of MII and the relationship of its structure to its specificity for the α3β2 subtype of the neuronal nicotinic acetylcholine receptor (nAChR). Based on the correlation of structure to biological activity, the discovery of the 3-dimensional structure enables the design of α-4/7 conotoxin peptide analog, peptide mimetics and non-peptide mimetics which demonstrate specificity to different subtypes of neuronal nAChRs In one embodiment, compounds are developed which demonstrate higher specificity to the α3β2 subtype of neuronal nAChR than the α3β4 subtype, such as evidence by MII. In a second embodiment, compounds are developed which demonstrate higher specificity to the α3β4 subtype of neuronal nAChR than the α3β2 subtype, such as evidence by several of the MII derivatives described herein.

The derivatives, peptide analogs, peptide mimetics and non-peptide mimetics of the present invention are useful as cardiovascular agents, gastric motility agents, urinary incontinence agents, anti-smoking agents and for treating or detecting small-cell lung carcinoma (SCLC).

A third aspect of the present invention is directed to the synthesis of mimetics, e.g., organic molecules based on the three-dimensional structure of MII which demonstrates the same or different specificity to neuronal nAChRs.

A fourth aspect of the present invention is directed to the synthesis of peptide analogs and peptide mimetics of MII with altered nicotinic AChR subtype specificity based on the identification of peptide fragments which define the activity and selectivity of the conopeptide MII and on its three-dimensional structure.

A fifth aspect of the present invention is directed to synthesis of mimetics, e.g., organic molecules based upon the overall structural activity information relating to MII.

A sixth aspect of the present invention also provides for computer programs for the expression (such as visual display) of the three-dimensional structure of MII or a peptide analog or peptide mimetic thereof, and further, a computer program which expresses the identity of each constituent of MII and the precise location within the overall structure of that constituent, down to the atomic level. There are many currently available computer programs for the expression of the three-dimensional structure of a molecule. Generally, these programs provide for inputting of the coordinates for the three-dimensional structure of a molecule; means to express (such as visually display) such coordinates, means to alter such coordinates and means to express an image of a molecule having such altered coordinates. In a further aspect, one may program NMR coordinates of the location of the atoms of an MII molecule in three dimension space, wherein such coordinates have been obtained from NMR analysis of said MII molecule, into such programs to perform comparative protein modeling of MII or a portion thereof, as described herein. Also provided, therefore, is a computer program for the expression of the three-dimensional structure of a peptide analog or peptide mimetic of MII. Preferred is the computer program CAVEAT, available from Molecular Simulations, Inc. (Waltham, MA) with the coordinates as set forth in Figure 8 input.

BRIEF DESCRIPTION OF THE FIGURES

The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Figure 1 shows the effect of alanine substitutions in the conopeptide MII on the ability of the analogs to block acetylcholine-gated currents in voltage-clamped *Xenopus* oocytes expressing cloned rat α3 and β2 subunits.

Figure 2 shows the NOESY spectrum (250-ms mixing time) of α-CT_X MII in H_2O illustrating sequential NOE connectives between neighboring α and amide protons. The $d_{\alpha N}$ NOE cross peaks are connected by lines and are labeled by residue number. Two traces between residues Cys^2 - Asn^5 and Val^7 - Cys^{16} are shown with their contiguous connectives broken at Pro^6.

Figure 3 shows an amino acid sequence of α-CT_X MII with its disulfide bridges drawn to show its disulfide bridge pattern and a summary of short- to medium-range sequential NOE cross peaks as well as experimentally measured $^3J_{NH\text{-}C\alpha H}$ coupling constants. Arrows pointing down are those with ^3J constants <5.0 Hz, and those pointing up are those with ^3J constants >8.0 Hz. Filled bars represent the NOE cross peaks with the thickness classifying NOE intensities from strong (thick) to weak (thin) and the width indicating short- to medium-range separation along the linear sequence. *** represents overlapped NOE cross peaks.

Figure 4 shows α proton chemical shift differences (ppm), between observed values from α-CT_X MII in H_2O and random-coil values, plotted versus the residue.

Figures 5A-B show superimposition of the 14 lowest energy structures of α-CT_X MII calculated from simulated annealing.

Figure 6A-C show the angular order parameters for the backbone obtained from the 14 minimum energy structures, plotted versus the residue number. Figure 6A shows parameters for ϕ; Figure 6B for ψ; and Figure 6C for χ.

Figure 7 shows surface (A,B) and backbone (C, D, E) representations of α-CT_X MII, PnIA, and GI. Space-filling models of the X-ray crystal structure of α-CT_X PnIA (A) and the lowest energy structure of α-CT_X MII (B) are displayed in purple for hydrophobic residues, in yellow for polar side chains and in red (positive) and blue (negative) for charged side chains. Backbone conformations of α-CT_X PnIA (C), α-CT_X MII (D), and α-CT_X GI (E) are displayed in ribbons and surface distributions in dots with the same color codes to illustrate their similarity and difference. Arrows indicate terminal residues, blue for carboxyl and yellow for amino.

Figure 8 lists the coordinates of α-conotoxin MII. These coordinates have been deposited in the Brookhaven Protein Data Bank, Upton, NY 19973, under accession code 1m2c.

Figure 9 shows selective block by α-Conotoxin MII of α3β2 nAChRs. Oocytes expressing various nAChR subunit combinations were voltage-clamped and the response to ACh was measured at various α-Conotoxin MII concentrations. Data represent the mean ± S.E. for at least three oocytes at each concentration.

Figure 10 shows that block of α3β2 nAChRs by α-Conotoxin MII is independent of the membrane potential. Oocytes expressing α3β2 nAChRs were voltage-clamped and the response to ACh was measured over a range of membrane potentials. Peak-amplitude currents in the absence (○) and presence (▲) of 500 pM α-Conotoxin MII are plotted against the membrane potential. Scaled toxin responses (▼) are also shown.

Figure 11A-C show that the competitive antagonist, Dihydro-β-Erythroidine (DHβE), protects α3β2 nAChRs from blockade by α-Conotoxin MII. Oocytes expressing α3β2 nAChRs were voltage-clamped and the response to ACh was measured. In Figure 11A, 500 μM DHβE was applied for 5 min. The oocyte was then continuously perfused with buffer without DHβE. In Figure 11B, 500 μM DHβE was applied for 5 min. followed by coapplication of 500 μM DHβE and 20nM α-Conotoxin MII for 2 min. The oocyte was then continuously perfused with buffer without toxins. In Figure 11C, 20 nM α-Conotoxin MII was applied for 2 min. The oocyte was then continuously perfused with buffer without toxin.

Figure 12A and B show the kinetics of block of α3β2 and α3β4 nAChRs by α-Conotoxin MII. Figure 12A shows the response of voltage-clamped oocytes expressing α3β2 nAChRs to ACh measured during application of 500 pM α-Conotoxin MII (first graph) and following washout from toxin (second graph). Figure 12B shows the response of voltage-clamped oocytes expressing α3β4 nAChRs to ACh measured during application of 1 μM α-Conotoxin MII (first graph) and following washout from toxin (second graph).

Figure 13A and B show the recovery kinetics of α3β2 and α3β4 nAChRs from block by saturating concentrations of α-Conotoxin MII. Figure 13A shows voltage-clamped oocytes expressing α3β2 nAChRs and their response to ACh. 2 μM α-conotoxin MII was applied for 5 min. The oocyte was then continuously perfused with buffer without toxin. Figure 13B shows oocytes expressing α3β4 nAChRs, which were voltage-clamped and their response to ACh. 2.5 mM α-Conotoxin MII was applied for 5 min. The oocyte was then continuously perfused with buffer

without toxin. Data were fit to a 2-site model (solid lines). Dashed lines represent the expected single-exponential recovery kinetics.

Figures 14A-C show the MII "Dock & Lock" model of ligand/receptor interation. In this illustration, MII binds at the interface between the α and β subunits. MII interacts with the β subunit with a very fast k_{on} and k_{off} and thus moderate affinity. Conversly, MII interacts with the α subunit with a very slow k_{on} and k_{off} and thus moderate affinity. As shown in Fig. 14A and 14B, MII approaches the receptor and very rapidly binds to the β subunit (docking interaction). However, this rapid binding to the β subunit in close proximity to the α subunit binding site leads to enhancement of the rate of MII's interaction with the α subunit and subsequent blockage of the receptor. Fig. 14C shows that once MII is bound to the α subunit, it has a very slow k_{off} (locking interaction). Thus, by targeting the subunit interface of the nicotinic receptor, MII is able to convert two relatively moderate binding interactions into a very potent and specific interaction with one molecular form of neuronal nAChR.

SUMMARY OF SEQUENCE LISTING

SEQ ID NO:1 is the amino acid sequence for α-CT_X MII peptide.

SEQ ID NO:2 is the amino acid sequence for derivatives of the alpha conopeptide MII.

SEQ ID NO:3 is the amino acid sequence for the FATN chimera of MII.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Derivatives of MII

The present invention relates to derivatives of MII, an α-4/7 conotoxinpeptide, in which amino acid residues are substituted as described herein while maintaining the basic activity of MII. More specifically, the present invention is directed to the derivatives having the general formula (SEQ ID NO:2):

Xaa-Cys-Cys-Xaa-Xaa_1-Xaa_2-Xaa-Cys-Xaa_3-Xaa-Xaa_4-Xaa_5-Xaa-Xaa-Xaa-Cys,

wherein Xaa represents an amino acid selected from the group consisting of natural, modified or non-natural amino acids. The modifications may be by addition substitution or deletion of one or more amino acid residues. The modification may also include the addition or substitution of analogs of the amino acid themselves, such as peptidomimetics, or amino acids with altered side groups, or mimetics, e.g., organic molecules with similar space/structure/function relationships. Individual residue Xaa_1 is any amino acid, preferably Asn or His; Xaa_2 is any amino acid, preferably Pro or

hydroxy-Pro; Xaa_3 is any amino acid, preferably His or Asn; Xaa_4 is any amino acid, preferably Glu; and Xaa_5 is preferably His or Asn. It is most preferred that Xaa_1 is Asn; Xaa_2 is Pro or hydroxy-Pro; and Xaa_3 is His. The derivatives contain two disulfide bonds between the first and third cysteine residues and between the second and fourth cysteine residues. The C-terminal end may contain a carboxyl or amide group, preferably an amide group. The amino acid is an α-amino acid, which includes natural amino acids, including unusual amino acids such as γ-carboxyglutamic acid, as well as modified or non-natural amino acids, such as those described in, for example, Roberts et al. (1983).

The derivatives of the present invention are highly selective for either the α3β2 or α3β4 subtype of neuronal nAChRs which are present in the autonomic and central nervous systems. Thus, they are useful as cardiovascular agents, gastric motility agents, urinary incontinence agents and anti-smoking agents, as well as being useful against SCLC.

The conopeptides can be produced by recombinant DNA techniques well known in the art. Also, these conopeptide derivatives are sufficiently small to be chemically synthesized. General chemical syntheses for preparing the foregoing conopeptide derivatives are described hereinafter, along with specific chemical synthesis of conopeptide derivatives and indications of biological activities of these synthetic products. The conopeptides of the present invention may be synthesized and/or substantially pure. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and preferably at least about 95% purity.

II. Preparation of recombinant and chemically synthesized derivatives.

The conopeptides of the present invention can be produced by recombinant DNA techniques well known in the art., such as those described in, for example, Sambrook et al. (1979). The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct disulfide bonds, if present in the final molecule.

One method of forming disulfide bonds in the conopeptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the elution of the native material

or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. It is also found that the linear peptide, or the oxidized product having more than one fraction, can sometimes be used for *in vivo* administration because the cross-linking and/or rearrangement which occurs *in vivo* has been found to create the biologically potent conopeptide molecule. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they can be chemically synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology. Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ-carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an a-amino group on an amino acid or a fragment while that entity reacts at the carboxyl group, followed by the selective removal of the a-amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the amino acid residues

located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the a-amino groups during the synthesis. However, for some amino acids, e.g., His, protection is not generally necessary. In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the a-amino protecting group at each step of the synthesis, and © the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

While solution phase synthesis may be used, peptides are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected a-amino acid to a suitable resin. Such a starting material can be prepared by attaching an a-amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or para-methylbenzhydrylamine (MBHA) resin. Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966). Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-terminus. Thus, solid resin supports may be any of those known in the art, such as one having the formulae -O-CH_2-resin support, -NH BHA resin support, or -NH-MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in Horiki et al. (1978), using KF in DMF at about 60° C for 24 hours with stirring, when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the a-amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride (CH_2Cl_2) or TFA alone. The deprotection is carried out at a temperature between about 0° C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific a-amino protecting groups may be used as described in Schroder and Lubke (1965).

After removal of the a-amino-protecting group, the remaining a-amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HoBt or HoAt).

The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder and Lubke (1965) and Kapoor (1970).

Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF):CH_2Cl_2 (1:1) or in DMF or CH_2Cl_2 alone. In cases where intermediate coupling occurs, the coupling procedure is repeated before removal of the a-amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent such as liquid hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all

remaining side chain protecting groups and also the a-amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0°C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

The conopeptide derivatives of the present invention may possess biological activity different from MII or may demonstrate the same or varying degrees of the same biological activity as MII which is known to block native $\alpha 3\beta 2$-containing nAChRs and with lower potencies, $\alpha 3\beta 4$ containing nAChRs (U.S. Patent 5,780,433 incorporated herein by reference), as well as other activities described herein.

III. Three-Dimensional Structure of MII

A. Overview

Another aspect of the present invention is directed to the discovery of the 3-dimensional structure of MII and the relationship of its structure to its specificity for the $\alpha 3\beta 2$ subtype of the neuronal nicotinic acetylcholine receptor (nAChR). The discovery of the 3-dimensional structure enables the design of α-4/7 conotoxin peptide analogs and peptide mimetics which will demonstrate the same specificity to neuronal nAChR. Such analogs and peptide mimetics are useful as cardiovascular agents and for treating or detecting small-cell lung carcinoma (SCLC).

MII has the following amino acid sequence (SEQ ID NO:1):

Gly-Cys-Cys-Ser-Asn-Pro-Val-Cys-His-Leu-Glu-His-Ser-Asn-Leu-Cys.

The C-terminus may contain a carboxyl or amide group, preferably an amide group. The amino acid at position 6 may be proline or 4-trans-hydroxyproline, preferably proline.

The identification of MII is described in U.S. Patent 5,514,774 and U.S. Patent 5,780,433, incorporated herein by reference. The use of MII for: (a) treating a patient having small-cell lung carcinoma (SCLC); (b) inhibiting SCLC proliferation; (c) detecting the presence of SCLC tumors, and (d) detecting the location of SCLC tumors is described in application U.S. Patent 5,595,972, incorporated herein by reference. The use of MII to treat CNS disorders is described in U.S. Patent 5,780,433, incorporated herein by reference. The use of MII as a cardiovascular agent is described in U.S. Serial No. 60/031,141, filed 18 November 1996, incorporated herein by reference.

B. Determination of the peptide three-dimensional structures using NMR.

Different techniques give different and complementary information about protein structure. The primary structure is obtained by biochemical methods, either by direct determination of the amino acid sequence from the protein, or from the nucleotide sequence of the corresponding gene or cDNA. NMR methods may be employed to obtain the secondary and tertiary structure, which requires detailed information about the arrangement of atoms within a protein.

NMR methods use the magnetic properties of atomic nuclei. Certain atomic nuclei, such as ^{1}H, ^{13}C, ^{15}N, and ^{31}P have a magnetic moment or spin. The chemical environment of such nuclei can be probed by nuclear magnetic resonance, NMR, and this technique can be exploited to give information on the distances between atoms in a molecule. These distances can then be used to derive a three-dimensional model of the molecule. Most structure determinations of protein molecules by NMR have used the spin of ^{1}H, since hydrogen atoms are abundant in proteins.

When protein molecules are placed in a strong magnetic field, the spin of their hydrogen atoms aligns along the field. This equilibrium alignment can be changed to an excited state by applying radio frequency (RF) pulses to the sample. When the nuclei of the protein molecule revert to their equilibrium state, they emit RF radiation that can be measured. The exact frequency of the emitted radiation from each nucleus depends on the molecular environment of the nucleus and is different for each atom, unless they are chemically equivalent and have the same molecular environment. These different frequencies are obtained relative to a reference signal and are called chemical shifts. The nature, duration and combination of applied RF pulses can be varied enormously and different molecular properties of the sample can be probed by selecting the appropriate combination of pulses.

In principle, it is possible to obtain a unique signal (chemical shift) for each hydrogen atom in a protein molecule, except those that are chemically equivalent, for example, the protons on the CH_3 side chain of an alanine residue. In practice, however, such one-dimensional NMR spectra of

protein molecules contain overlapping signals from many hydrogen atoms because the differences in chemical shifts are often smaller than the resolving power of the instrument. This problem has been overcome by designing experimental conditions that yield a two-dimensional NMR spectrum, the results of which are usually plotted in a diagram. The diagonal in such a diagram corresponds to a normal one-dimensional NMR spectrum. The peaks off the diagonal result from interactions between hydrogen atoms that are close to each other in space. By varying the nature of the applied RF pulses, these off-diagonal peaks can reveal different types of interactions.

Two-dimensional experiments consist of discreet elements: a preparation period; an evolution period where spins are "labeled" as they process in the xy plane according to their chemical shift; a mixing period, during which correlations are made with other spins; and a detection period, where a free induction decay is recorded.

Experiments are distinguished by the nature of the correlation that are probed during the mixing period. A COSY (correlation spectroscopy) experiment gives peaks between hydrogen atoms that are covalently connected through one or two other atoms, for example, the hydrogen atoms attached to the nitrogen and Cα atoms within the same amino acid residue. For amino acids with a single H^{β} proton, a standard double quantum filtered COSY (DQF-COSY) recorded in D_2O may be used. However, for amino acids with a β-methylene group, modified COSY experiments such as P.E. COSY, is better suited. Nuclear overhauser effect spectroscopy (NOESY), on the other hand, gives peaks between pairs of hydrogen atoms that are close together in space even if they are from amino acid residues that are quite distant in the primary sequence. In total correlation spectroscopy (TOCSY), correlations are observed between all protons which share mutual coupling partners, whether or not they are directly coupled to each other.

Two dimensional NMR spectra of proteins are interpreted by the method of sequential assignment. Obviously, two-dimensional NOE spectra, by specifying which groups are close together in space, contain three-dimensional information about the protein molecule. It is far from trivial, however, to assign the observed peaks in the spectra to hydrogen atoms in specific residues along the polypeptide chain because the order of peaks along the diagonal has no simple relation to the order of amino acids along the polypeptide chain. This problem has in principle been solved in the laboratory of Kurt Wüthrich in the E.T.H., Zürich, where the method of sequential assignment was invented.

Sequential assignment is based on the differences in the number of hydrogen atoms and their covalent connectivity in the different amino acid residues. Each type of amino acid has a specific

set of covalently connected hydrogen atoms that will give a specific combination of cross-peaks, a "fingerprint." in a COSY spectrum. From the COSY spectrum, it is therefore possible to identify the H atoms that belong to each amino acid residue and, in addition, determine the nature of the side chain of that residue. However, the order of these fingerprints along the diagonal has no relation to the amino acid sequence of the protein.

The sequence-specific assignment, however, can be made from NOE spectra that record signals from H atoms that are close together in space. In addition to the interactions between H atoms that are far apart in the sequent, these spectra also record interactions between H atoms from sequentially adjacent residues. These signals in the NOE spectra therefore in principle make it possible to determine which fingerprint in the COSY spectrum comes from a residue adjacent to the one previously identified.

In practice, it is difficult to make unique assignments for longer pieces than di- or tri-peptides, since NOE signals also occur between residues close together in space but far apart in the sequence. Therefore, the peptide segments that have been uniquely identified by NMR are usually matched with corresponding segments in the independently determined amino acid sequence of the protein. NMR spectroscopy identifies H atoms in the protein that are close together in space, and this information is then used to derive, indirectly, a three-dimensional model of the protein.

Distance constraints can be used to derive possible structures of a protein molecule. The result of the sequence-specific assignment of NMR signals, preferably done using interactive computer graphics, is a list of distance constraints from specific hydrogen atoms in one residue to hydrogen atoms in a second residue. The list contains a large number of such distances, which are usually divided into three intervals within the region 1.8 Å to 5 Å, depending on the intensity of the NOE peak. This list immediately identifies the secondary structure elements of the peptide or protein molecules because both α helices and β sheets have very specific sets of interactions of less than 5 Å between their hydrogen atoms. It is also possible to derive models of the three-dimensional structure of the molecule. In order to obtain a more qualitative picture of conformations of a peptide and to generate three-dimensional structures compatible with NMR data, the principles of simulated annealing (Nilges, M. (1988)) may be employed. Simulated annealing calculations carry out an extensive search for all possible three-dimensional conformations that satisfy given experimental data (e.g., NOE-derived distances and dihedral angles) and root mean square (RMS) deviation (described herein) is used as a measure of degree of convergence among those calculated structures.

C. Description of MII Structure

Even though α-CT_X MII is a small peptide made of only 16 amino acid residues, it has a well-defined three-dimensional solution structure. In addition to two disulfide bridges which form a hydrophobic Cys knot, there are three helical regions in the structure which contribute to form a very tight conformation. The presence of such stable secondary structures and disulfide bridges allows the multidimensional NMR method to be effective in obtaining a very high resolution structure of the peptide. The amino-terminal region has almost a full turn of α-helix (Cys^2 - Ser^4); this is followed by Asn^5 which has backbone dihedral angles of $\phi = -89°$ and $\psi = +132°$ (measured from the minimum energy structure), thereby essentially making a 90° turn. The helix with almost two turns (Pro^6 - Glu^{11}) is the major secondary structural component of the peptide. This helix is terminated by His^{12} ($\phi = -136°$, $\psi = +77°$; measured from the minimum energy structure) which orients the remaining C-terminal distorted 3_{10} helix (Ser^{13}-Cys^{16}) toward the N-terminus. These two turns associated with Asn^5 and His^{12} are perhaps critical residues for the overall fold of the peptide and the presence of such turns is further supported by Cα proton shift data presented in Figure 4 (positive shifts compare to the rest having negative shifts) as well as well as $^3J_{NH\text{-}C\alpha}$ coupling constants in Figure 2 (>8.0 Hz coupling constants compare to the rest having <5.0 Hz). A possible function of Asn^5 is to induce a turn between the N-terminal segment and the main α-helix; this function is consistent with the survey by Richardson and Richardson (Richardson, J.S. (1988)) of 215 α-helices from 45 different globular protein structures. They reported a striking preference of 3.5:1 for Asn at the N-cap position and 2.6:1 for Pro at the N-cap + 1 position (helix initiator) for α-helices. With respect to the second turn around His^{12}, the function of His may be to bring Cys^3 and Cys^{16} close together to form the second disulfide bridge.

The space-filling model of α-CT_X MII shown in Figure 7B is oriented to explore the surface distribution of hydrophobic and hydrophilic side chain groups of the molecule. Hydrophobic residues are colored purple to distinguish them from polar residues which are yellow, or charged residues which are red (positive) and blue (negative). A flat surface located on top of the molecule in purple is a distinct structural feature representing the cluster of hydrophobic residues exposed to solvent. This hydrophobic surface is formed largely by Gly^1 (excluding the N-terminal amino group), Cys^2, Cys^3, Leu^{15}, Cys^{16} and the disulfide bond between Cys^3 and Cys^{16}. This flat surface may be important for ligand-receptor binding through hydrophobic interactions. There is another very distinct surface that consists entirely of hydrophilic residues with both polar and charged groups. On the left side of the model, the cluster of red, blue and yellow represents a region of the

turn at His^{12} (Glu^{11}-Asn^{14}). This highly charged surface, almost perpendicular to the hydrophobic surface, could be responsible for its initial recognition by nAChR based on long-range electrostatic attractions. This potential receptor-binding interface is composed of sequential residues Glu^{11}, His^{12}, Ser^{13} and Asn^{14}.

In view of the above analysis and the Examples which follow, the conceptually important structural features unique to nAChR targeting α-4/7 conotoxins can be summarized as follows:

(1) There are two disulfide bridges between the first and third cysteine and the second and fourth cysteine. Several isoforms generated with different disulfide pairings have been tested for their activity towards the nAChRs and shown *not* to retain the native activity.

(2) There is a central α-helix consisting of six residues starting precisely at the position i+3 where i is the second cysteine residue and ending at j+3 where j is the third cysteine residue. It is believed that this α-helix is essential for the overall backbone conformation and, in particular, its length (six amino acids in MII) and helical pitch are identified as critical features for targeting nAChRs. NMR data from an α-4/7 conotoxin MII mutant suggests that the mutation causes the central helix to further extend beyond the j+3 position towards the C-terminal end and thereby causing its helical pitch to change. This structural change is associated with the loss of activity by three orders of magnitude.

(3) Two turns at both the N and C terminal ends (N- and C-caps) of the central helix are also unique structural features found in this class of conotoxins. They are intimately linked with the central helix to dictate the three dimensional folding motif and their positions are i+2 for the N-cap where i is the second cysteine residue and j+4 for the C-cap where j is the third cysteine. Based on the primary sequence comparison among the sequenced α-4/7 conotoxins, there appears to be some preference for both N– and C-cap positions. These are asparagine, which is a good hydrogen bonding partner, and histidine and tyrosine, which are sterically bulky aromatic residues. For example, there are 3.5:1 preference for Asn at the N-cap position from 215 α-helices subjected for studies by Richardson J.S. et al. (1988). It has been found that mutations at these positions in conotoxins results in the loss of their functions by three orders of magnitude.

(4) Proline residue at position i+3 where i is the second cysteine residue is conserved among all α-4/7 conotoxins. Its structural role is mostly likely to prevent continuation of the central helix in the amino terminal direction due to its sterically hindering ring structure.

(5) Analysis of the kinetics of binding of MII indicate that this peptide has two distinct binding surfaces which interact with the α and β subunit of the nAChR. NMR analysis is consistent

with this and indicates that one MII face is hydrophobic in nature consisting of residues *i*-2, *i*-1, *i* (where *i* is the second cysteine residue), *j*+7 (where *j* is the third cysteine) and the fourth cysteine, and the disulfide bond between the second and fourth cysteine residues. The other face is hydrophilic in nature and consists of residues *j*+3, *j*+4, *j*+5 and *j*+6 where *j* is the third cysteine. Mutational analysis indicates that the hydrophilic face is particularly important for peptide on-rate (peptide docking) and the hydrophobic face is particularly important for peptide off-rate (peptide locking). The use of two physically distinct peptide surfaces to interact with adjacent α and β receptor subunits represents a specific strategy for designing ligands selective for receptors with different combinations of α and β subunits.

IV. Interaction of MII with nAChRs

MII achieves its remarkable subtype specificity through double-faced interacting with the receptor. MII's rank order of potency suggests that MII interacts with both α and non-α subunits of nAChRs. Block by MII is consistent with competitive inhibition as evidenced by voltage-independence of MII's activity and the ability of competitive antagonist dihydro-β-erythroidine to interfere with MII's ability to block the receptor. The shape of the time course recovery curve following block of α3β2 and α3β4 receptors by high concentrations of MII indicates that each of these receptors has two binding sites for MII, and occupancy of either site by toxin blocks receptor function. There appears to be a general pattern of two ligand binding sites for α/non-α subunit combinations of neuronal nAChRs. This is in contrast to α7 homomeric receptors which may have up to five Ach binding sites. Rates of recovery following block by MII are markedly longer for α3-containing receptors than for receptors with no α3 subunits. However, the IC_{50} for MII's block of α3β2 receptors is approximately 4 orders of magnitude lower than that of α3β4 receptors. Remarkably, MII's off-rate is essentially the same for both receptor subtypes and the IC_{50} difference is almost entirely accounted for by a difference in MII's on-rate. Taken together, the data suggest that MII's on-rate is largely controlled by its interaction with the β subunit whereas interaction with the α subunit is primarily responsible for MII's off-rate. The kinetics of a synthetic chimera of MII support this conclusion (Example 10). MII's selective actions can be accounted for by a "dock and lock" model (Example 12).

The 3-dimensional solution structure of MII taken together with the data discussed in detail herein leads to a two-step dock-and-lock mechanism to explain the remarkable subtype specificity of MII. The NMR structure suggests that MII is a roughly wedge-shaped peptide with a hydrophilic

edge and a hydrophobic edge. The four amino-acids of α-conotoxin MII (HLEH) which were substituted to FATN are all located on the hydrophilic edge of the peptide. The results with the FATN analog, and the kinetic results obtained with wild-type toxin acting on the α3β2 nicotinic receptor are thus suggestive that the docking face of the toxin is located on the hydrophilic side of the wedge, and that this hydrophilic face interacts with a fast on-time with the β2 subunit. The other side of the wedge which is characterized by hydrophobic residues exposed to solvent, would be an attractive locus for the locking face of α-conotoxin MII, which is postulated to interact with high affinity on a site on the α3 subunit of nAChR targets of this peptide. A cartoon representation of α-conotoxin MII interacting with the α3β2 and α3β4 receptors, and of the FATN-α-conotoxin MII analog is shown in Figure 14.

The differential on and off rates for MII can be used to develop an assay to screen compounds for nAChR antagonistic activity and receptor subtype specificity. The on and off rates for the binding of MII and a compound to be screened to the α3β2 and α3β4 subunits are determined and compared. If the on rate for the compound is greater than or equal to the on rate for MII with respect to the α3β2 subtype, the on rate for the compound is less than or equal to the on rate for MII with respect to the α3β4 subtype and the off rates for the compound are greater than or equal to the off rates for MII , then the compound is a nAChR antagonist and specific for the α3β2 subtype. If the on rate for the compound is less than or equal to the on rate for MII with respect to the α3β2 subtype, the on rate for the compound is greater than or equal to the on rate for MII with respect to the α3β4 subtype and the off rates for the compound are greater than or equal to the off rates for MII, then the compound is a nAChR antagonist and specific for the α3β4 subtype.

In addition, compounds can be developed which modulate the activity of neuronal nAChRs having α3β2 or α3β4 subtype specificity based on the three dimensional structure of MII as disclosed herein, the structure/biological activity of MII disclosed herein and molecular modeling analysis. Thus, in accordance with the present invention, compounds are developed which modulate the activity of neuronal nAChRs and which have subtype specificity for either the α3β2 or α3β4 subtype.

V. Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptides or compounds with which they interact (agonists, antagonists, inhibitors, binding partners, etc.). By creating such analogs, it is possible to fashion drugs which are more active or

stable than the natural molecules, which have different susceptibility to alteration or which may affect the function of various other molecules. In one approach, one would generate a three-dimensional structure for MII, such as described herein, or by computer modeling, or by a combination of both approaches. An alternative approach, "alanine scan," involves the random replacement of residues throughout molecule with alanine, and the resulting affect on function determined.

It also is possible to isolate an MII specific antibody, selected by a functional assay, and then solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallograph altogether by generating anti-idiotypic antibodies to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of anti-idiotype would be expected to be an analog of the original antigen. The anti-idiotype could then be used to identify and isolate peptides from banks of chemically- or biologically-produced peptides. Selected peptides would then serve as the pharmacore. Anti-idiotypes may be generated using the methods described herein for producing antibodies, using an antibody as the antigen.

Thus, one may design drugs which have improved MII activity or which act as stimulators, inhibitors, agonists, antagonists or MII or molecules affected by MII function. In addition, knowledge of the polypeptide sequences permits computer employed predictions of structure-function relationships.

A substance identified as a modulator of polypeptide function may be peptide or non-peptide in nature. Non-peptide "small molecules" are often preferred for many *in vivo* pharmaceutical uses. Accordingly, a mimetic or mimic of the substance (particularly if a peptide) may be designed for pharmaceutical use.

The designing of mimetics to a known pharmaceutically active compound is a known approach to the development of pharmaceuticals based on a "lead" compound. This might be desirable where the active compound is difficult or expensive to synthesize or where it is unsuitable for a particular method of administration, e.g., pure peptides are unsuitable active agents for oral compositions as they tend to be quickly degraded by proteases in the alimentary canal. Mimetic design, synthesis and testing is generally used to avoid randomly screening large numbers of molecules for a target property.

There are several steps commonly taken in the design of a mimetic from a compound having a given target property. First, the particular parts of the compound that are critical and/or important

in determining the target property are determined. In the case of a peptide, this can be done by systematically varying the amino acid residues in the peptide, e.g., by substituting each residue in turn. Alanine scans of peptide are commonly used to refine such peptide motifs. These parts or residues constituting the active region of the compound are known as its "pharmacophore".

Once the pharmacophore has been found, its structure is modeled according to its physical properties, e.g., stereochemistry, bonding, size and/or charge, using data from a range of sources, e.g., spectroscopic techniques, x-ray diffraction data and NMR. Computational analysis, similarity mapping (which models the charge and/or volume of a pharmacophore, rather than the bonding between atoms) and other techniques can be used in this modeling process.

In a variant of this approach, the three-dimensional structure of the ligand and its binding partner are modeled. This can be especially useful where the ligand and/or binding partner change conformation on binding, allowing the model to take account of this in the design of the mimetic.

A template molecule is then selected onto which chemical groups which mimic the pharmacophore can be grafted. The template molecule and the chemical groups grafted onto it can conveniently be selected so that the mimetic is easy to synthesize, is likely to be pharmacologically acceptable, and does not degrade *in vivo*, while retaining the biological activity of the lead compound. Alternatively, where the mimetic is peptide-based, further stability can be achieved by cyclizing the peptide, increasing its rigidity. The mimetic or mimetics found by this approach can then be screened to see whether they have the target property, or to what extent they exhibit it. Further optimization or modification can then be carried out to arrive at one or more final mimetics for *in vivo* or clinical testing.

VI. Designing Biologically Active Molecules Based on Structure of MII

A. Overview

In general, biologically active molecules exert their effect by binding to a receptor. The ability of a given molecule to bind to a receptor is determined by the presence of certain important functional groups and the three-dimensional (3D) presentation of these features by the molecule. A goal of molecular modeling in the context of designing bioactive molecules is to understand the determinants of receptor binding and to sue this knowledge in the design or discovery of novel molecules with the desired activity. The availability of structure-activity data or the structure of a receptor enables the proposal of a pharmacophoric pattern which, in the best case, would include the functionality required for activity and the relative orientation of the functional groups. (Gund,

1979). Recent advances in techniques for generating 3D molecular structures for typical drug-sized organic molecules and for searching databases of 3D structures combined with a 3D pharmacophore hypothesis give the medicinal chemist new tools that can assist in discovering novel active molecules. A 3D pharmacophore can be used as a query to search a database of molecules for those that are predicted to possess the desired activity if the pharmacophore hypothesis is correct. If a receptor structure or receptor site model is available, another type of 3D searching can be used. For this, molecules are selected based on their steric and chemical match to the receptor structure, without the need to propose which interactions might be most important. The methods are complementary and both have assisted in the discovery of active molecules.

The significance of the HLEH fragment of MII has been investigated and its biological activity and receptor binding has been correlated to its structural, chemical and physical attributes (features). These features are used to help understand the range of biological activity observed in a series of compounds, as well as to help guide the design of new compounds with potentially different affinities for nicotinic nAChRs, e.g., compounds with higher affinity for the $\alpha 3\beta 2$ subtype or compounds with higher affinity for the $\alpha 3\beta 4$ subtype.

A wide range of experimental and theoretical data is routinely used to develop patterns of such features. This process is generally referred to as pharmacophore mapping and involves three main aspects: finding the features required for biological activity; determining the molecular conformation required (i.e., the "bioactive" conformation); and developing a superposition or alignment rule for the series of compounds. The primary information used in pharmacophore mapping is derived naturally from the compounds synthesized in a series and their measured biological activity. From this, structure-activity relations emerge and rudimentary pharmacophore hypotheses can begin to be formulated. If the structure of the macromolecular target or target-ligand complex is known, either as determined experimentally or as computationally modeled, this information is obviously very useful to the pharmacophore-mapping process. A variety of molecular-modeling and computational chemistry techniques can then be applied, in conjunction with the experimental data, to develop pharmacophore models. These techniques range from simple, qualitative molecular graphics comparisons of several members in a series to sophisticated, quantitative methodologies for generating pharmacophore maps and measuring their ability to reproduce experimental results.

Pharmacophore mapping is largely a *qualitative* exercise. Allied with pharmacophore mapping is the field of three-dimensional *quantitative* structure-activity relations (3D-QSAR). 3D-

QSAR techniques attempt to derive and investigate quantitative models of biological activity; namely, models that fit the potency of the studied compounds and that can be used to predict the potency of compounds outside the study set. In fact, the application of many 3D-QSAR methods requires a proposed pharmacophore model.

Pharmacophore mapping has its roots in traditional medicinal chemistry and the structure-activity relations derived from the synthesis and biological testing of series of compounds. From the relative measured potencies of individual members of a series, a picture of the types of functionality, and perhaps their spatial relations that are important for activity, begins to emerge. More detailed molecular-modeling studies can then be used to formulate a more rigorous model but even in their absence proposed pharmacophore hypotheses can begin to take shape.

Many ligand-design studies employ molecular modeling as well as chemical synthesis to help elucidate pharmacophoric patterns. Structure-activity data and the conformational analysis results are used to propose a bioactive conformation and superposition rule for the series. This may be done by using molecular graphics.

Another common approach in pharmacophore mapping is the use of structurally rigid molecules to probe requirements for receptor binding. One of the advantages of using less conformationally flexible molecules is that they can more exactly define the bioactive conformation, provided that the rigid molecules selected show good affinity. Use of rigidification to better define pharmacophore space has been used successfully in generating active nonpeptidic compounds from peptide leads. Ku, et al. (1995) and co-workers' recent work with nonpeptide compounds based on cyclic RGD peptide analogues is a good example of this.

Receptor site mapping encompasses a variety of computational procedures that identify energetically favorable binding sites on macromolecules. The most straightforward procedures involve "painting" a solvent-accessible surface (or an otherwise generated cast) of the macromolecular target according to empirically determined physical properties, such as electrostatic or lipophilic potential, degree of curvature, and hydrogen-bonding character. Such methods for thus characterizing the surface of a macromolecule are incorporated in programs such as Grasp (Columbia University), DelPhi (Biosym Technologies), MOLCAD (Tripos. Inc.), and Hint (Virginia Commonwealth University). Subsequent molecule design involves identification or design of ligands that possess features complimentary to the identified surface characteristics. More advanced algorithms involve the actual calculation of interaction enthalpies between the target and potential ligands or fragments. In practice, the coordinates of the protein or protein fragment of interest

(which may be rotated or otherwise transformed) are stripped of any undesired ligand (or portion thereof) and/or of any undesired solvent molecules. The coordinates are then processed to attach molecular mechanics parameters to the atomic positions to provide a processed target for mapping. The target may be partitioned into discrete binding sites. The target or partitioned sites thereof are flooded with given functional group fragments that are subsequently allowed to relax into desired locations, as in the program MCSS (Molecular Simulations, Inc.), or are encased within a regular lattice of site points on which single fragment probes are positioned sequentially; examples of programs that exploit the site-lattice algorithm include Grin/Grid (Molecular Discovery, Ltd.), Ludi (Biosym Technologies), Leapfrog (Tripos, Inc.), and Legend (University of Tokyo). In both techniques, the enthalpic contribution to binding affinity is estimated with a molecular mechanics force-field, and appropriate positions of selected functional groups are determined systematically.

In the site-lattice approach, a box is defined enclosing a desired portion of the target within a defined lattice. The lattice resolution, i.e., the distance between lattice points, may be defined by the practitioner or may be set by the computer program. Likewise, the other parameters of points within the lattice, such as hydrophobicity or other characteristics, may be similarly defined. Probes (i.e., computer models) of one or more selected moieties, functional groups, molecules or molecular fragments are positioned at lattice points and the interaction energy of the probe-target pair is determined for each such lattice point. The data for each selected moiety, functional group, etc. is collected and may be recovered as a data set, visualized on a computer monitor or printed out in various text or graphic formats.

As an alternative to positioning a moiety at each of a set of lattice points, one may, as previously mentioned, flood the target (defined by the coordinates as described above) with multiple copies of a selected fragment, moiety, molecule, etc. by superimposing the multiple copies into the vicinity of the protein target. The model is then subjected to group minimization (i.e., molecular mechanics minimization) calculations to identify points or areas of favorable interaction. Data may be handled as in the lattice approach.

Receptor site maps provide the seeds for ligand evolution via Database searches, which are described above, and for Grow/link methods for *de Novo* design of new chemical entities. Programs for ligand growth first access extensible fragment dictionaries in order to place appropriate functional groups at site points. A genetic algorithm or a subgraph isomorphism protocol is then invoked to connect the fragments with small aliphatic chains or rings. Stochastic enhancements may be introduced by modification of internal degrees of freedom as well as translation and rotation of

the candidate model within the binding cavity. The resulting sets of molecules are scored and filtered by functions that consider the steric constraints of the binding site, the complimentarity of electrostatic and hydrophobic interactions, and a solvation estimate. Programs of this type that could be applied include Ludi (Biosym Technologies), Leapfrog (Tripos, Inc.), Legend (University of Tokyo), Grow (Upjohn), Builder/Delegate (University of California, San Francisco), and Sprout (University of Leeds). Clique detection methods provide an alternative strategy to site mapping and ligand growth. DOCK (University of California, San Francisco) and similar programs fill a given binding site with the smallest set of atom-sized spheres possible; a database search then attempts to orient ligands such that the atoms superimpose onto the centers (or "nuclei") of the site-filling spheres. The shape complimentarity of augmented by scoring functions that include the steric requirements of the cavity and a potential energy function.

Optimization of ligands (from any source) may be enhanced using the three dimensional structural of MII. Use of receptor site maps or hydropathic profiles of MII may be used to identify preferred positions for functional group components of ligands, and can be used to filter or constrain conformational searches of ligand structures which would otherwise typically be controlled by minimal steric considerations of the ligand structures themselves. The availability of an explicit binding site also permits one to determine the mode of ligand binding to the target protein via methods that utilize force-fields directly in simulated annealing, distance geometry, Metropolis Monte Carlo, or stochastic searches for binding modes. Examples of programs that can be applied to rationalize ligand binding include Autodock (Scripps Clinic), DGEOM (QCPE #590), Sculpt (Interactive Simulations, Inc.), or any of the molecular dynamics programs described above. Once a tractable set of possible binding orientations is obtained, one can readily identify the appropriate mode of binding through modifications in test ligands designed to alter in a predictable fashion the binding affinity of each model under consideration. For instance, a ligand may be modified to contain a functional group at a position which is inconsistent with one binding model, yet consistent with another model. Binding data can then be used to weed out "disproven" models. Once iterative weeding of unlikely binding modes generates an appropriate model, possibilities for improvement of the lead become readily apparent from the local protein environment.

An alternative protocol for ligand optimization involves 3D database searching in conjunction with knowledge of the binding site. Modeling can reveal multiple candidates for the bioactive conformation of a given ligand. A probe for the correct conformation can include a 3D search to identify several constrained mimics of each possible conformer. Structure-activity

relationships of the unconstrained ligand would suggest which functional groups should be retained in the constrained mimics. Finally, the steric and electrostatic requirements of the binding site could constitute a filter for prioritizing the resultant possibilities.

The structure of MII permits accurate model-building of homologous peptides and their subsequent use in drug design. The MII structure may be readily used in the development of a reliable model by either knowledge-based template building methods, or by iterations of directed point mutations followed by local molecular mechanics minimizations. Examples of programs that can be applied in the development of a model of Syk-NC include Composer (Birbeck College), Modeler (MSI), and Homology (Biosym Technologies). The resultant model can then be subjected to any of the CADD techniques described above.

B. Utilization of the structure of the α-conotoxin MII in computer-aided drug design.

The availability of the three-dimensional structure of the α-conotoxin MII makes structure-based drug discovery approaches possible. Structure-based approaches include *de Novo* molecular design, computer-aided optimization of lead molecules, and computer-based selection of candidate drug structures based on structural criteria. New pepidomimetic modules may be developed directly from the structure of the peptide ligand by design or database searches for conformationally-restricted peptide replacements. Alternatively, structure-based lead discovery may be accomplished using the target protein structure, e.g. receptor, stripped of its ligand.

Multiple uncomplexed states of MII can be generated by several methods to provide additional target conformations. The experimental coordinates and the resulting uncomplexed models can be subjected to techniques such as receptor site mapping to identify sites of favorable interaction energies between the structure of the target protein and potential ligands or chemical moieties ("fragments" or "seeds"). Such evaluation may be followed by procedures such as fragment seed linking and growth. Fragment seed linking refers to methods for designing structures that contain "linked" "seeds," i.e. chemical structures comprising two or more of the mapped moieties appropriately spaced to reach the respective sites of favorable interactions. Growth refers to the design of structures which extend, based on receptor site mapping or to fill available space, a given molecule or moiety. Based on the receptor site mapping data, one may also select potential ligands from databases of chemical structures. Potential ligands, or suboptimal ligands, of whatever source, can be refined by using the receptor site maps to filter multiple ligand conformations and orientations according to energetic preferences. The structure of MII permits one to generate a high-quality model of MII by either knowledge-based homology template methods or iterative site-

mutations followed by minimizations. The generated structure of MII may then be treated as an additional protein target by the methods outlined above. These methods and their application to MII are described in the sections that follow.

The amino acid sequence of α-conotoxin MII has been determined (Cartier, et al., 1996) and the determinants for specificity (specific amino acid residues) for MII on α3β2 neuronal nicotinic receptors have been identified (Harvey, et al., 1997, incorporated herein by reference). Knowledge of the determinants and the binding orientation of a peptide can suggest avenues for conformational restriction and peptide bond replacement. A less biased approach involves computer algorithms for searching databases of three-dimensional structures to identify replacements for one or more portions of the peptide ligand, preferably non-peptidic replacement moieties. By this method, one can generate compounds for which the bioactive conformation is heavily populated, i.e., compounds which are based on particularly biologically relevant conformations of the peptide ligand. Algorithms for this purpose are implemented in programs such as Cast-3D (Chemical Abstracts Service), 3DB Unity (Tripos, Inc.) and MACCS/ISIS-3D (Molecular Design Limited). These geometric searches can be augmented by steric searching, in which the size and shape requirements of the binding site are used to weed out hits that have prohibitive dimensions. Programs that may be used to synchronize the geometric and steric requirements in a search applied to MII include CAVEAT (University of California, Berkeley).

By way of illustration, a non-exclusive list of computer programs for performing rigid three-dimensional searches include the following:

3Dsearch (Seridan, r.p. et al., J. Chen. Inf. Comput. Sci. 29:255. 1989)

Aladdin (Van Drie, J.H. et al., J. Comput. Aided Mol. Design 3:225. 1989)

UNITY (Tripos, Inc.)

MACCS-3D (MDL)

CATALYST (Biosyn/MSI, Inc.)

All of these searching protocols may be used in conjunction with existing corporate databases, the Cambridge Structural Database, or available chemical databases from chemical suppliers.

As practitioners in this art will appreciate, various computational analyses may be used to determine the degree of similarity between the three-dimensional structure of a given peptide and MII (or a portion or complex thereof) or another α-conotoxin peptide or portion or complex thereof such as are described herein. Such analyses may be carried out with commercially available

software applications, such as CAVEAT (Molecular Simulations, Inc., Waltham, MA) as described by Lauri and Bartlott (1994).

CAVEAT is a program that uses a database search to assist in the design of novel molecules. It is a special-purpose program that was written to aid in the design of small molecules that could mimic a protein loop important in a protein-protein interaction. The basic assumption of the programs is that protein-protein recognition is based on specific positioning of amino acid side chains and that the backbone is not critical and could be replaced. The CAVEAT program attempts to find ring systems that can present the side chains in the desired orientation. A CAVEAT database consists of the distance and angle relations of vectors, defined by the exocyclic bonds of ring systems, and an index back to the 3D structure of the ring. A typical query might define the Cα-Cβ vector relations that would be required to present the necessary side chain analogues. Such a vector search could be conducted by most generic database-searching programs discussed in this chapter; however, CAVEAT is optimized for this task. Although the initial CAVEAT applications were for protein mimicry, the program could be useful in any situation for which one needed a novel scaffold to present a set of functional groups in a defined orientation. The latest CAVEAT suite of programs includes the ability to cluster the hits, based on size or substructure similarity, and to rank hits by size, number of atoms at ring fusions, and whether the designed molecule would have eclipsing interactions. Two novel databases are available for use with CAVEAT: Triad, a computer-generated collection of all tricyclic hydrocarbons, and Iliad, a collection of acyclic molecules. Software is also available to create CAVEAT databases from the Cambridge Structural Database.

In addition to the retention of potential pharmacophoric elements that are present in the peptide explicitly, the incorporation into a ligand structure of hydrogen-bond donating or accepting groups that can displace ordered water molecules usually provides a significant entropic gain that leads to a favorable free energy of binding. Such ordered waters are identifiable from the structure, and other ordered waters may be located during computer simulations of a fully solvated structure.

Structural coordinates of the peptides of this invention may be stored in a machine-readable form on a machine-readable storage medium, e.g. a computer hard drive, diskette, DAT tape, etc., for display as a three-dimensional shape or for other uses involving computer-assisted manipulation of, or computation based on, the structural coordinates or the three-dimensional structures they define. In order to use the structural coordinates generated for MII as set forth in Figure 8, it is often necessary to display them as, or convert them to, a three-dimensional shape, or to otherwise manipulate them. This is typically accomplished by the use of commercially available software such

as a program which is capable of generating three-dimensional graphical representations of molecules or portions thereof from a set of structural coordinates. By way of illustration, a non-exclusive list of computer programs for viewing or otherwise manipulating protein or peptide structures include the following:

Midas (University of California, San Francisco)
MidasPlus (University of California, San Francisco)
MOIL (University of Illinois)
Yummie (Yale University)
Sybyl (Tripos, Inc.)
Insight/Discovery (Biosym Technologies)
MacroModel (Columbia University)
Quanta (Molecular Simulations, Inc.)
Cerius (Molecular Simulations, Inc.)
Alchemy (Tripos, Inc.)
LabVision (Tripos, Inc.)
Rasmol (Glaxo Research and Development)
Ribbon (University of Alabama)
NAOMI (Oxford University)
Explorer Eyechem (Silicon Graphics, Inc.)
Univision (Cray Research)
Molscript (Uppsala University)
Chem-3D (Cambridge Scientific)
Chain (Baylor College of Medicine)
O (Uppsala University)
GRASP (Columbia University)
X-Plor (Molecular Simulations, Inc.; Yale University)
Spartan (Wavefunction, Inc.)
Catalyst (Molecular Simulations, Inc.)
Molcadd (Tripos, Inc.
VMD (University of Illinois/Beckman Institute)
Sculpt (Interactive Simulations, Inc.)
Procheck (Brookhaven National Laboratory)

DGEOM (QCPE)
RE_VIEW (Brunel University)
Modeller (Birbeck College, University of London)
Xmol (Minnesota Supercomputing Center)
Protein Expert (Cambridge Scientific)
HyperChem (Hypercube)
MD Display (University of Washington)
PKD (National Center for Biotechnology Information, NIH)

For example, data defining the three-dimensional structure of an α-conotoxin peptide, or portions or structurally similar homologs or analogs of MII, may be stored in a machine-readable storage medium and may be displayed as a graphical three-dimensional representation of the peptide structure, typically using a computer capable of reading the data from said storage medium and programmed with instructions for creating the representation from such data. This invention thus encompasses a machine, such as a computer, having a memory which contains data representing the structural coordinates of a composition of this invention, e.g. the coordinates set forth in Example 8, together with additional optional data and instructions for manipulating such data. Such data may be used for a variety of purposes, such as the elucidation of other related structures and drug discovery (WO 97/08300).

In comparative protein modeling, a first set of such machine readable data may be combined with a second set of machine-readable data using a machine programmed with instructions for using the first data set and the second data set to determine at least a portion of the coordinates corresponding to the second set of machine-readable data. For instance, the first set of data may comprise a Fourier transform of at least a portion of the coordinates for MII set forth in Figure 8, while the second data set may comprise coordinates for a potential analog of MII. In this manner, one may use molecular replacement to exploit a set of coordinates such as set forth in Figure 8 to determine the effect on the structure of such a replacement.

Therefore, another object of the invention is to provide a method for determining the three-dimensional structure of a peptide analog or peptide mimetic of MII using comparative protein modeling techniques and structural coordinates for a composition of this invention. Comparative protein modeling involves constructing a model of an unknown structure using structural coordinates of one or more related peptides. Comparative protein modeling may be conducted by

fitting common or homologous portions of the protein or peptide whose three-dimensional structure is to be solved to the three-dimensional structure of known homologous structural elements. Comparative protein modeling can include rebuilding part or all of a three-dimensional structure with replacement of amino acids (or other components) by those of the related structure to be solved. For example, using the structural coordinates of MII, one may determine the three dimensional structure of a peptide analog of MII using comparative protein modeling. Those coordinates may be stored, displayed, manipulated and otherwise used in like fashion as the MII coordinates of Example 8.

This invention further provides for the use of the structural coordinates of a peptide of this invention, or portions thereof, to identify reactive amino acids, such as cysteine residues, within the three-dimensional structure, preferably within or adjacent to a receptor binding site; to generate and visualize a molecular surface, such as a water-accessible surface or a surface comprising the space-filling van der Waals surface of all atoms; to calculate and visualize the size and shape of surface features of the peptide; to locate potential H-bond donors and acceptors within the three-dimensional structure, preferably within or adjacent to a receptor binding site and to calculate regions of hydrophobicity and hydrophilicity within the three-dimensional structure, preferably within or adjacent to a receptor binding site. One may use the foregoing approaches for characterizing the peptide and its interactions with a receptor to design or select compounds of complementary characteristics (e.g., size, shape, charge, hydrophobicity/hydrophilicity, receptor specificity, etc.) to surface features of the peptide, a set of which may be preselected. Using the structural coordinates, one may also predict or calculate the orientation, binding constant or relative affinity of the peptide to a given receptor subtype in the bound state, and use that information to design or select compounds of improved or altered affinity.

In such cases, the structural coordinates of the α-conotoxin peptide, or portion thereof, are entered in machine readable form into a machine programmed with instructions for carrying out the desired operation and containing any necessary additional data, e.g. data defining structural and/or functional characteristics of a potential analog, defining molecular characteristics of the various amino acids, etc.

Compounds of the structures selected or designed by any of the foregoing means may be tested for their ability to bind to an nAChR, inhibit the binding of an nAChR to a natural or non-natural ligand therefor, and/or inhibit a biological function mediated by an nAChR.

This invention also provides peptidomimetic and mimetic methods for designing a compound capable of binding to an nAChR. One such method involves graphically displaying a three-dimensional representation based on coordinates defining the three-dimensional structure of MII or a portion thereof bound to an nAChR. Interactions between portions of an MII and the receptor are characterized in order to identify candidate moieties for replacement. One or more portions of MII which interact with the receptor may be replaced with substitute moieties selected from a knowledge base of one or more candidate substitute moieties, and/or moieties may be added to MII to permit additional interactions with the receptor.

The computational approaches and structural insights disclosed herein, also permit the design or identification of molecules with *reduced* capacity, or substantial *inability*, to bind to an nAChR subtype. For example, one may apply the same modeling and computational methods to the data described herein, but with the opposite goal, i.e., to design or identify compounds which *lack* substantial binding affinity to one or more nAChR subtypes. Such information can be useful in research efforts aimed at identifying antagonists of a single subtype of nAChR. Compounds first identified by any such methods are also encompassed by this invention.

For storage, transfer and use with such programs of structural coordinates for a crystalline substance of this invention, a machine-readable storage medium is provided comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, e.g. a computer loaded with one or more programs of the sort identified above, is capable of displaying a graphical three-dimensional representation of any of the molecules or molecular complexes described herein. Machine-readable storage media comprising a data storage material include conventional computer hard drives, floppy disks, DAT tape, CD-ROM, and other magnetic, magneto-optical, optical, floptical and other media which may be adapted for use with a computer.

Even more preferred is a machine-readable data storage medium that is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex that is defined by the structural coordinates of MII or portion thereof, and in particular, structural coordinates of MII set forth in Fig. 8 ± a root mean square deviation from the backbone atoms of the amino acids of such protein of not more than 1.5 Å. An illustrative embodiment of this aspect of the invention is a conventional 3.5" diskette, DAT tape or hard drive encoded with a data set, preferably in PDB format, comprising the coordinates of Fig. 8.

In another embodiment, the machine-readable data storage medium comprises a data storage material encoded with a first set of machine readable data which comprises the Fourier transform of the structural coordinates set forth in Appendix I. Appendix II or Appendix III (or again, a derivative thereof), and which, when using a machine programmed with instructions for using said data, can be combined with a second set of machine readable data comprising the X-ray diffraction pattern of a molecule or molecular complex to determine at least a portion of the structural coordinates corresponding to the second set of machine readable data. Examples of systems useful for this aspect of the present invention are shown in WO/97/08300.

VII. Definitions

The present invention employs the following definitions.

"Biological Activity" is used herein to broadly denote function.

"Derivative" refers to an amino acid sequence wherein one or more residue of the natural sequence is substituted.

"Features" of a compound include any combination of structural, physical or chemical attributes of the compound which are required to elicit a certain biological activity.

A peptide **"fragment," "portion"** or **"segment"** is a stretch of amino acid residues of at least about two contiguous amino acids, typically at least about three contiguous amino acids and, most preferably, at least about four or more contiguous amino acids.

"Neuronal nAChR" refers to a natural nicotinic acetylcholine receptor found in the CNS.

"Peptide Analog(s)" refers to molecules which have more, fewer, different or modified residues from an α-conotoxin amino acid sequence. The modifications may be by addition, substitution or deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The analogs may possess functions different from natural α-conotoxin molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or increased stability or be easier to formulate. From time to time herein, the present analogs are referred to as proteins or peptides for convenience, but contemplated herein are other types of molecules, such as peptidomimetics or chemically modified peptides. A peptide analog may be referred to herein as a peptide for convenience.

"Peptide mimetic or mimetic" is intended to refer to a substance which has the essential biological activity of an α-conotoxin peptide. A peptide mimetic or mimetic may be a peptide-containing molecule that mimics elements of peptide secondary structure (Johnson et al., 1993). The underlying rationale behind the use of peptide mimetics or mimetics is that the peptide backbone exists chiefly to orient amino acid side chains in such a way as to facilitate molecular interactions, such as those of ligand and receptor. A peptide mimetic is designed to permit molecular interactions similar to the natural molecule. A mimetic may not be a peptide at all, but it will retain the essential biological activity of a natural conotoxin peptide.

"Related Composition" refers to compositions comprising a conotoxin peptide analog or peptide mimetic as an active ingredient.

"Simulated annealing" refers to a strategy for superimposing flexible molecules to investigate potential alignments.

"Substantially pure" refers to a peptide which is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and most preferably at least about 95% purity.

"Substantially similar activity" refers to the activity of a modified peptide, with reference to a natural α-conotoxin peptide. The modified peptide will have substantially similar activity. The modified peptide may have an altered amino acid sequence and/or may contain modified amino acids. In addition to the similarity of activity, the modified polypeptide may have other useful properties, such as a longer half-life. Alternatively, the similarity of activity of the modified peptide may be higher than the activity of the natural α-conopeptide. The modified peptide is synthesized using conventional techniques or is encoded by a modified nucleic acid and produced using conventional techniques. The modified nucleic acid is prepared by conventional techniques. A nucleic acid with an activity substantially similar to the natural α-conotoxin gene function may be used to produce the modified peptide described above.

"Subtype of nAChR" refers to different molecular forms of nicotinic acetylcholine receptors.

VIII. Preparation of peptide analogs and mimetics.

Peptide analogs and peptide mimetics of the present invention specific for the α3β2 or α3β4 subtypes of the nAChR, are prepared on the basis of procedures described herein, using conventional techniques, such as drug modeling, drug design and combinatorial chemistry. Suitable techniques

include, but are not limited to those described in U.S. Patent 5,571,698, U.S. Patent 5,514,774, WO 95/21193 (Ecker, et al. (1995); Persidis (1997); Johnson et al. (1993); Sun et al. (1993)) and the references cited therein which are all incorporated herein by reference. The development of peptide analogs and peptide mimetics are prepared using commercially available drug design software, including those set forth in Persidis et al. (1997). These peptide analogs and peptide mimetics have the substantially similar activities as an α-conotoxin described herein and in the published literature.

IX. Preparation of pharmaceutical compositions containing peptide analogs and mimetics

Pharmaceutical compositions containing a compound of the present invention as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques, such as those in *Remington's Pharmaceutical Sciences* (1990). Typically, an antagonistic amount of the active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques.

For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

The active ingredients, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can be prepared synthetically for each active ingredient on the basis of the developed sequences and the known genetic code.

The active ingredients of the present invention are administered in an amount sufficient to generate the desired effect. The dosage range at which these agents exhibit this effect can vary widely, depending upon the severity of the patient's defect, the patient, the route of administration and the presence of other underlying disease states within the patient. Typically, the active ingredients exhibit their therapeutic effect at a dosage range from about 0.05 mg/kg to about 250 mg/kg, and preferably from about 0.1 mg/kg to about 100 mg/kg of the active ingredient. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved.

EXAMPLES

The present invention is further detailed in the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art of the techniques specifically described below are utilized.

EXAMPLE 1

Synthesis of α-Conotoxin MII and MII Derivatives

MII, originally isolated from *Conus magus*, was chemically synthesized using standard Fmoc chemistry on an ABI model 431 peptide synthesizer and properly folded to its biologically active conformation using two-step oxidation protocols (Monje et al., 1993). Once purified, the peptide's identity with the native MII was confirmed as described by Cartier et al., 1996.

MII derivatives were chemically synthesized and folded in the similar manner. Initial derivatives were prepared with alanine substitutions for each non-cysteine amino acid residue, (i.e., an alanine walk) in order to determine the effect of substitutions at each residue. Additional

derivatives or analogs are prepared in the similar manner by substituting any amino acid for the amino acid residues of MII except the cysteine and His_{12} amino acid residues.

EXAMPLE 2

Biological Activity of α-Conotoxins MII and MII Derivatives, Peptide Analogs and Peptide Mimetics

Each of the MII derivatives, peptide analogs and peptide mimetics were tested for activity on neuronal nAChRs in *Xenopus laevis* oocytes containing the α3 and β2 subunits of nAChRs as described by Cartier et al. (1996). Briefly, oocytes (1-2 days after harvesting) were injected with cRNA encoding the α3 and β2 subunits of rat nAChRs and incubated at 25° C for 1-4 days prior to use. Electrophysiological currents were measured using conventional techniques, such as described in Cartier et al. (1996). Measurements were made for oocytes perfused with acetylcholine as controls and for oocytes incubated with either MII or the analogs prepared in Example 1.

Figure 1 shows the effect of alanine substitutions in the conopeptide MII on the ability of the analogs to block acetylcholine-gated currents in voltage-clamped *Xenopus* oocytes expressing cloned rat α3 and β2 subunits. Most substitutions decreased MII's potency 4-fold or less. The notable exceptions are: Glu_{11}: 8-fold decrease; His_5: 25-fold decrease; His_{12}: $>10^4$-fold decrease. In addition, it was seen that Asn_5 (which can be substituted with His) and Pro_6 along with His_{12} (which can be substituted with Asn) were essential for high affinity binding to the α3β2 nAChR. Similar effects are seen when other amino acids are substituted for the various residues of MII. The more conservative the substitution of amino acid residues in the analogs, the more similar the activity which is seen for the synthesized analogs. Sequences of several α-conotoxins and their biological activity is shown in Shon et al. (1997).

EXAMPLE 3

NMR Spectroscopy

NMR Spectroscopy. A sample containing 8 mg. of the peptide was dissolved in 500 μL of 5mM sodium phosphate buffer made of 90% H_2O and 10% D_2O (Cambridge Isotope Laboratory). The final pH of the peptide solution was 3.3, and the peptide concentration was 9.4 mM. For experiments requiring "100%" replacement of labile amide hydrogens with deuterons, the sample was lyophilized and dissolved in D_2O (99.96% isotope enriched). After being allowed to sit

overnight at room temperature, the sample was again lyophilized and dissolved in D_2O (99.996% isotope enriched).

All NMR data were obtained with a Varian 600 MHZ Unity Plus spectrometer equipped with a pulsed-field-gradient (*z*) unit. A set of 2-D ^1H NMR experiments were carried out at 275 K: these were NOESY (Jeener, J. (1979); Kumar, A. (1980); Macura, S. (1981)) with mixing times of 75, 150, 250 and 350 ms, TOCSY (Braunschweiler, L. (1983); Davis, D.G. (1985)) with a mixing time of 64 ms, DQF-COSY (Piantini, U. (1982); Rance, M. (1983)) and PE-COSY (Muller, L. (1987)). All spectra were recorded in a phase sensitive mode (States, D.J. (1982)) with a spectral width of 6600 Hz and 4K data points except for PE-COSY (8K data points). Eight to 32 scans were signal averaged for each free induction decay (FID) with a relaxation delay of 2 s; each 2-D experiment was completed with 400-512 FIDs. In NOESY experiments, the solvent signal was suppressed by gradient echo combined with the WATERGATE sequence (Piotto, M. (1992)). A "flip-back" pulse was inserted right after the mixing time to restore the residual magnetization along the *z*-axis. In TOCSY, a spin lock field of 7.7 kHz necessary for the coherence transfer among scalar-coupled ^1H spins was generated with the DIPSI-2 sequence (Rucker, S. (1989)), and water suppression was obtained using the WATERGATE sequence along with minimum presaturation set at the residual water signal during the relaxation delay. In PE-COSY, water suppression was not needed since the sample was prepared in 100% D_2O. A mixing pulse of 30° was used for PE-COSY, and each FID was recorded with 32 scans to compensation for the sensitivity loss due to the small mixing pulse.

2-D NMR data were transferred to an SGI workstation (Indigo^2) and were processed using Felix 95.0 (MSI, San Diego) except for PE-COSY, which was processed using VNMR 5.10 (Varian). FIDs were apodized with a window function (90° and 135° shifted sine bell) in both dimensions prior to Fourier transformation. Each Fourier transformed FID was baseline corrected by applying a third-order polynomial, and each dimension was referenced to a chemical shift value of 4.76 ppm at the residual water signal.

Even though complete resonance assignments were easily obtained except for the Cβ protons of Ser^{13} (not observed), the 1-D spectrum of the peptide in the amide proton region had a few resonance overlaps. Starting with the unique reside Val^7, identified on the basis of its spin type, sequential $d_{\alpha N}$ NOE connectivity was traced through the carboxyl terminal residue Cys^{16}. Along the trace, resonance assignment for each residue was confirmed on the basis of its spin type obtained from the TOCSY experiment. The remaining N-terminal residues were also assigned on the basis of sequential $d_{\alpha N}$ NOE connectivity starting from Asn^5, whose spin system was identified from NOE

cross peaks between its amide proton and β protons as well as its side chain γNH2 protons. In addition, sequential NOEs arising from neighboring amide protons, d_{NN}, confirmed the above resonance assignments. Figure 2 depicts two traces of sequential NOE $d_{\alpha N}$ connectivities which extend from Cys^2 to Asn^5 and from Val^7 to Cys^{16}.

EXAMPLE 4

Generation of Dihedral and Distance Restraints

NOE cross peak volumes were measured from NOESY data with four different mixing times using FELIX 95.0. NOE buildup curves were then fitted with a second-order polynomial and exact distances were generated for all assigned NOE cross peaks. A distance of 1.8 Å was used as an appropriate reference for nonoverlapping geminal Cβ proton cross peaks, as well as for lower distance bounds. Several volumes of nonoverlapping geminal Cβ proton cross peaks were averaged and used for calibrating measured NOE volumes. A pseudoatom correction of 1 Å (Wuthrich, K. (1983)) was added to the upper limits of those NOE cross peaks involving spectroscopically degenerate methyl and methylene protons. As for dihedral restraints, $^3J_{HN\text{-}H\alpha}$ coupling constants were measured from a 1-D ^1H spectrum recorded with 32K data points and converted to ϕ dihedral angles centered at -120° (±30°) for $^3J_{HN\text{-}H\alpha}$ >8.0 Hz and -60° (±30°) for $^3J_{HN\text{-}H\alpha}$ <5.0 Hz (Pardi, A., et al. (1984)). $^3J_{\alpha\beta}$ coupling constants were also measured form PE-COSY recorded from the sample whose amide protons were completely exchanged out with deuterons in "100%" D_2O. The measured $^3J_{\alpha\beta}$ coupling constants derived from those residues with an AMX spin system and with nonoverlapping geminal β protons were used for defining χ_1 dihedral angles in combination with the sequential $d_{HN\text{-}H\alpha}$ and $d_{\alpha\beta}$ NOE cross peak intensities (Hyberts, S. (1987); Wagner, G. (1987)).

Initially, 99 interresidue NOE cross peaks with a high level of confidence in their assignments were selected and corrected for those NOE cross peaks containing at least one pseudoatom. Fifteen chirality restraints and 11 ϕ and 5 χ_1 dihedral angles were also included in the restraint file for generating an initial set of 10 structures using the DGII (Havel, T. (1991)) module of the InsightII program (MSI, San Diego). All structures generated by the DGII calculations had similar overall backbone folding patterns, and thus the lowest energy structure with the minimum number of NOE violations was chosen and subjected to an iterative relaxation matrix approach (IRMA). This procedure improves the accuracy and precision of interproton NOE-derived distance restraints by evaluating the full relaxation network of spins in a molecule (Boelens, R. (1988). At this stage, the total of 158 NOE-derived interproton distances (including intraresidue NOEs with

pseudoatom correction) along with 16 dihedral angle and 15 chirality restraints were subjected to IRMA and restrained molecular dynamics (RMD) followed by energy minimization steps. Any distances derived from NOEs containing at least one pseudoatom were not treated by IRMA, and therefore those were not refined by the process. Each cycle of IRMA took experimental NOE intensities measured as a function of mixing time and merged them with the calculated theoretical NOE intensity values for the model structure. A new set of distance restraints was then deduced from this mixed NOE intensity matrix. A rotational correlation time of 1.5 ns, estimated from NOE buildup curves of nonoverlapping geminal β protons, and diagonal leakage rate of 1.0 s were used in each IRMA cycle. After each cycle of IRMA, the structure was subjected to RMD and energy minimization steps using a Lennard-Jones potential with a 12.0 Å cutoff. Five cycles of 1,000 steps of RMD of 1.0 fs for a duration of 5 ps was calculated at 700 K followed by cooling over 5 ps at 500 k and another 5 ps at 300 K. The structure was minimized using 100 steps of steepest descents followed by 1500 steps of conjugated gradient minimization. Four IRMA/RMD cycles were carried out and the convergence was achieved with the final R-factors (a measure of the difference in the theoretical and experimental NOE intensities) reaching 0.407 for R_1 and 0.007 for R_6 (reflects $1/r^6$ relationship between NOE intensity and distance, r) (Gonzales, C. (1991)). This IRMA/RMD protocol is well documented in the manual provided by the InsightII software for refining distances converted from experimentally measured NOE cross peaks.

It was obvious from both $^3J_{NH\text{-}C\alpha}$ coupling constants recorded from a high-resolution 1-D spectrum and short- and medium-range NOE cross peaks from NOESY experiments that a large portion of the peptide was helical. Nine of 16 residues were determined to have $^3J_{NH\text{-}C\alpha}$ coupling constants of less than 5.0 Hz and among those nine resides we have identified short- and medium-range NOE cross peaks, d_{NN}, $d_{NN(I, I+2)}$, $d_{\alpha N}$, and $d_{\alpha N(I, I+2)}$, very typical of an *α-helix* (Wuthrich, K. et al. (1986)). Figure 2 displays those NOE cross peaks according to their intensities along with $^3J_{NH\text{-}C\alpha}$ coupling constants used to generate dihedral angle restraints. In addition to the observed NOE cross peaks, Cα proton chemical shifts relative to random-coil values (Wuthrich, K. et al. (1986)) are a good assessments for identifying local helical components in peptides and proteins (Wishart, D.S. et al. (1991); Rothemund, S. et al. (1996)). The plot shown in Figure 4 strongly suggests that the peptide contains a large portion of helical conformation throughout the sequence except for residues Asn[5] and His[12]. The backbone conformation of these residues could deviate from a helical conformation on the basis of their positive shifts in the plot.

EXAMPLE 5

Molecular Modeling, Distance Geometry and Simulated Annealing

Computer models of α-CT_x MII were constructed and manipulated using the InsightII and Discover programs (MSI, San Diego) on a Silicon Graphics workstation. Simulated annealing (SA) computations were conducted on a Cray C-90 supercomputer at the San Diego Supercomputer Center. The consistent valence force field of Hagler and co-workers (Dauber-Osguthorpe, P. (1988)) was employed for both the DGII and simulated annealing calculations. An extended molecule with two disulfide bridges was constructed as the triply charged cation with full positive charges on the N-terminal nitrogen and the imidazole side chains of His^9 and His^{12}.

A triangle inequality bound smoothing and four-dimensional embedding procedure followed by prospective metrication and majorization with a constant weighting scheme was used for DGII calculations with default settings except for an initial energy of 750 kcal/mol and 20,000 steps of built-in simulated annealing with a step size of 0.3 ps.

In order to develop a more qualitative picture of the conformation(s) of α-CT_x MII and to generate three-dimensional structures compatible with the NMR data, a protocol based generally on the principles of simulated annealing as developed by Clore and Gronenborn and co-workers (Nilges, M. (1988)) was employed. The calculations incorporated two notable departures from previous work. First, the interproton distances were introduced in a biphasic manner during high-temperature molecular dynamics (MD); initially they involved only backbone protons, but then subsequently they involved side chain protons. Second, transition from a quartic to a Lennard-Jones nonbonded potential was achieved in a final dynamics phase concomitant with final maturation of the nonbond energy factor. A total of 50 rounds of SA were conducted in order to sample as large a conformational space as practical given computer processor and disk limitations. A final minimization with a convergence criterion of the large derivative not exceeding 0.01 kcal mol^{-1} $Å^{-1}$ was conducted.

A total of 50 structures resulted from the SA calculations were described using 154 distance (85 intraresidue, 42 sequential, 22 medium range and 5 long range), 14 dihedral and 15 chirality restraints. An RMS deviation-based family clustering scheme was used which resulted in the grouping of these structures into 30 families spanning the energy range 396-5360 kcal/mol with the two families of lowest energy encompassing 18 of the 50 structures. Structural statistics of these five families, with minimum energy structure (MES) energies within 22 kcal/mol of the overall MES are given in Table 1. The next lowest energy family (family 3) was at 79 kcal/mol relative to the

overall MES. By interactive graphical inspection, we have observed that many of the higher energy family representatives (families 3-30) contained unusually high internal energy terms or pathological features (e.g., broken bonds, knots involving backbone and cystine bridges). An interesting structural pathology is observed in structure 8 of family 1 (PDB accession code 1m2c) wherein $_{L}$-α-Cys^{8} is inverted to $_{D}$-α-Cys^{8}. This structure is included because it fits the criterion used for classifying family 1 but in no way influenced the final model and underscores the important of maintaining proper chirality constraints during SA.

In Figure 5, the structures of family 1 were superimposed to demonstrate how well they converge in the structural calculations with a given set of experimentally determined and refined restraints. As shown in Table 1, the pairwide backbone and heavy atom RMS deviations among those 14 structures in family 1 calculated over residues Cys^{2}-Cys^{16} (Gly^{1} is excluded due to its mobility) are 0.76 ± 0.31 and 1.35 ± 0.34 Å, respectively. In the SA procedure, no particular restrains was employed to force backbone amide bonds to the transconfiguration. All amides bonds in all residues of all structures in this family are trans, and all 14 structures in family 1 have almost the same backbone dihedral angles with the exception of Gly^{1}, as seen from high values of the backbone angular order parameters (Hyberts, S. et al (1992); Pallaghy, P. et al (1993)). in Figure 6A,B. However, this consistency of the backbone dihedral angles is not maintained at the level of the χ_1 side chain dihedral. High angular order parameters as seen in Figure 6C for residues 2, 5, 9 and 10 indicate that all structures of family 1 have equivalent side chain rotameric states. All other residues have multiple side chain rotameric states which generally fall into the *gauche*$^{-}$, *gauche*+, or *trans* classification. The structures of family 1 are well built as judged by the range and magnitude of the energetic contributions detailed in Table 1. Clearly, important energetic contributions to the maintenance of these structures are found in the nonbonded terms, both van der Waals and Coulombic. These modeling studies were conducted *in vacua*, and any modulation of the effective dielectric constant by either empirical solvation methods or explicitly solvent inclusion should serve only to decreasc the net effect of electrostatics for this simple constrained peptide.

TABLE 1

Structural Statistics for the Two Lowest Energy Families of MII Resulting from Simulated Annealing

family	1	2
no. of structures	14	4
energy components [a]		
E_{total}	453±30	476±48
E_{bond}	28±2	28±1
E_{angle}	161±12	165±14
$E_{torsion}$	50±6	63±14
$E_{out\ of\ plane}$	4±1	4±1
$E_{van\ der\ Waals}$	75±8	84±17
$E_{Coulomb}$	135±9	132±9
E_{force}	75±20	77±21
$E_{total+force}$	527±47	553±68
pairwide RMS[b]		
backbone (2-16)	0.76±0.31	0.99±0.25
heavy atoms (2-16)	1.35±0.34	1.61±0.25
NMR violations >0.2Å[b]		
av no. of violations per structure	16.64±3.13	16.50±3.64
av violation	0.30±0.11	0.31±0.11
dihedral violations >10°	1/14[c] (Cys^2 χ_1)	1/4[d] (Cys^2 χ_1)
		2/4[d] (His^9 χ_1)
minimum energy structure		
E_{total}	396	418
$E_{total+force}$	440	463
no. of violations >0.2 Å	13	21
av violation >0.2 Å[b]	0.25±0.04	0.32±0.12
max violation[b]	0.35	0.66

[a]All energies in kcal/mol. [b]All distance in Å. [c]Number of structures in family 1. [d]Number of structures of a family 2.

EXAMPLE 6

Three Dimensional Solution Structure

Even though α-CT_X MII is a small peptide made of only 16 amino acid residues, it has a well-defined three-dimensional solution structure. In addition to two disulfide bridges which form a hydrophobic Cys knot. there are three helical regions in the structure which contribute to form a very tight conformation. The presence of such stable secondary structures and disulfide bridges allows the multidimensional NMR method to be effective in obtaining a very high resolution structure of the peptide. The amino-terminal region has almost a full turn of α-helix (Cys^2 - Ser^4); this is followed by Asn^5 which has backbone dihedral angles of $\phi = -89°$ and $\psi = +132°$ (measured from the minimum energy structure), thereby essentially making a 90° turn. The helix with almost two turns (Pro^6 - Glu^{11}) is the major secondary structural component of the peptide. This helix is termination by His^{12} ($\phi = -136°$, $\psi = +77°$; measured from the minimum energy structure) which orients the remaining C-terminal distorted 3_{10} helix (Ser^{13}-Cys^{16}) toward the N-terminus. These two turns associated with Asn^5 and His^{12} are perhaps critical residues for the overall fold of the peptide and the presence of such turns is further supported by Cα proton shift data presented in Figure 4 (positive shifts compare to the rest having negative shifts) as well as well as $^3J_{NH\text{-}C\alpha}$ coupling constants in Figure 2 (>8.0 Hz coupling constants compare to the rest having <5.0 Hz). A possible function of Asn^5 is to induce a turn between the N-terminal segment and the main α-helix; this function is consistent with the survey by Richardson and Richardson (Richardson, J.S. et al (1988)) of 215 α-helices from 45 different globular protein structures. They reported a striking preference of 3,5:1 for Asn at the N-cap position and 2.6:1 for Pro at the N-cap + 1 position (helix initiator) for α-helices. With respect to the second turn around His^{12}, the function of His may be to bring Cys^3 and Cys^{16} close together to form the second disulfide bridge.

The space-filling model of α-CT_X MII shown in Figure 7B is oriented to explore the surface distribution of hydrophobic and hydrophilic side chain groups of the molecule. Hydrophobic residues are colored purple to distinguish them from polar residues which are yellow, or charged residues which are red (positive) and blue (negative). A flat surface located on top of the molecule in purple is a distinct structural feature representing the cluster of hydrophobic residues exposed to solvent. This hydrophobic surface is formed largely by Gly^1 (excluding the N-terminal amino group), Cys^3, Cys^8, Leu^{15}, Cys^{16} and the disulfide bond between Cys^3 and Cys^{16}. This flat surface may be important for ligand-receptor binding through hydrophobic interactions. There is another very distinct surface that consists entirely of hydrophilic residues with both polar and charged

groups. On the left side of the model, the cluster of red, blue and yellow represents a region of the turn at His^{12} (Glu^{11}-Asn^{14}). This highly charged surface, almost perpendicular to the hydrophobic surface, could be responsible for its initial recognition by nAChR based on long-range electrostatic attractions. This potential receptor-binding interface is composed of sequential residues Glu^{11}, His^{12}, Ser^{13} and Asn^{14}.

EXAMPLE 7

Electrophysiology

cDNA clones encoding nAChR subunits were provided by S. Heinemann and D. Johnson (Salk Institute, San Diego, CA). cRNA was transcribed using RiboMAX™ large scale RNA production systems (Promega, Madison, WI). Diguanosine triphosphate (Sigma, St. Louis, MO) was used for synthesis of capped cRNA transcripts according to the protocol of the manufacturer. Plasmid constructs of mouse and rat nAChR subunits were as conventionally described: α1, β1, γ, δ; α2; α3; α4;α7; α9; β2; β4.

cRNA was injected with a Drummond 10 μl microdispenser (Drummond Scientific, Broomall, PA) using conventional techniques. It was fitted with micropipettes pulled rom glass capillaries provided for the microdispenser. The pipette tips were broken to an OD of 22-25 μm and back-filled with paraffin before mounting on the microdispenser. cRNA were drawn into the micropipette and 50 nl, containing 5 ng cRNA subunit, was injected into each oocyte. In the case of muscle subunits, 0.5-5 ng of each subunit was injected.

Oocytes were harvested from *Xenopus* frogs, cut into clumps of 20-50 oocytes, and placed in a 50 ml polypropylene tube (Sarstedt) containing 580 U/ml type 1 collagenase (Worthington Biochemical, Freehold, NJ) in OR-2 (82.5 mM Nacl, 2.0 MM KCl, 1.0 mM $MgCl_2$ and 5mM HEPES, pH ~7.3). The tube was incubated for 1-2 hr on a rotary shaker rotating at 50 rpm. Halfway through the incubation, the solution was exchanged with fresh collagenase solution. The oocytes were then washed with six to eight ~50 ml volumes of OR-2, transferred to a 60 mm x 15 mm petri dish containing ND-96 (96.0 mM Nacl, 2.0 mM KCl, 1.8 mM $CaCl_2$, 1.0 mM $MgCl_2$, 5mM HEPES, pH = 7.1-7.5)/Pen/Strep/Gen (100 U/ml penicillin G (Sigma), 100 μg/ml streptomycin (Sigma), and 100 μg/ml gentamycin (Gibco BRL, Grand Island, NY). The oocytes were visually examined and only healthy appearing oocytes were transferred to a second dish containing ND96 and antibiotics. Oocytes were injected 1-2 days after harvesting and recordings were made 1-7 days after injection.

An injected oocyte was placed in a ~30 μl recording chamber consisting of a cylindrical well (~4 mm dia x 2 mm deep) fabricated from Sylgard, and gravity-perfused with either ND96 or ND96 containing 1 μM atropine (ND96A) at a rate of ~1 ml/min. All toxin solutions also containing 0.1 mg/ml bovine serum albumin (BSA) to reduce nonspecific adsorption of peptide. The perfusion medium could be switched to one containing peptide or acetylcholine (ACh) by use of a distributor valve (SmartValve, Cavro Scientific Instruments, Sunnyvale, CA) and a series of three-way solenoid valves (model 161T031, Neptune Research, Northboro, MA). ACh-gated currents were obtained with a two-electrode voltage-clamp amplifier (model OC-725B, Warner Instrument Corp., Hamden, CT) set for "fast" clamp and with clamp gain at maximum (x 2000). Glass microelectrodes, pulled from fiber-filled borosilicate capillaries (1 mm OD x 0.75 mm ID, WPI Inc., Sarasota, FL) and filled with 3 M KCl, served as voltage and current electrodes. Resistances were 0.5 - 5 MΩ for voltage, and 0.5 - 2 MΩ for current, electrodes. The membrane potential was clamped at -70 mV, and the current signal, recorded through virtual ground, was low-pass filtered (5 Hz cut-off) and digitized at a sampling frequency of 20 Hz. The solenoid perfusion valves were controlled with solid state relays (model ODC5 in a PB16HC digital I/O backplane, Opto 22, Temecula, CA). A/D conversion and digital control of solenoid valves were performed with a Lab-LC or Lab-NB board (National Instruments, Austin, TX) in a Macintosh (Quadra 630 or IIcx) computer. The computer communicated with the distributor valve via its serial port. Data acquisition and activities of the distributor and solenoid valves were automatically controlled by a home-made virtual instrument constructed with the graphical programming language LabVIEW (National Instruments, Austin, TX).

To apply a pulse of ACh to the oocyte, the perfusion fluid was switched to one containing ACh for 1 sec. This was automatically done in intervals of 1-5 min. The shortest time interval was chosen such that reproducible control responses were obtained with no observable rundown. This time interval was dependent upon the nAChR subtypes being tested. The concentration of ACh was 1 μM for oocytes expressing α1βγδ, 1 mM for α7, and 300 μM for all others. The ACh was diluted in ND96A for all except α7, in which case the diluent was ND96. For control responses, the ACh pulse was preceded by perfusion with ND96 (for α7) or ND96A (all others). No atropine was used with oocytes expressing α7, since it has been demonstrated to be an antagonist of these receptors. (Gerzanich, 1994) For responses in toxin (test responses), the perfusion solution was switched to one containing toxin while maintaining the interval pulses of ACh. Toxin was continuously perfused until equilibrium was reached. All ACh pulses contained no toxin, for it was assumed that

little, if any, bound toxin would have washed away in the brief time (<2 sec) it takes for the responses to peak. The peak amplitudes of the ACh-gated current responses were measured by the virtual instrument. All recordings were made at room temperature (~22° C).

An injected oocyte was voltage-clamped at a membrane potential of -70 mV and response to ACh was measured every 5 min. After several control responses were determined at -70 mV, the membrane potential was stepped to the test potential for 1 min. beginning 10 sec. before application of ACh. The membrane potential was returned to -70 mV between each test. The test potential was varied, in sequence, from -90 mV to -10 mV in steps of 10 mV followed by a final test at a membrane potential of +10mV. After the test sequence, the perfusion solution was switched to one containing toxin. After equilibrium was achieved, the test sequence was repeated.

All data analysis was performed with Prism software (GraphPad Software Inc., San Diego, CA) running on an Apple Power Macintosh 6100/66 equip with a 486 Intel processor and Windows 3.1™. The average of three control responses just preceding a test response was used to normalize the test response to obtain "% response" or "% block."

Each data point of a dose response curve represents the average ± standard error of at least three oocytes. Dose response curves were fit to the equation:%Response = $100/(1+(\text{toxin})/IC_{50})^{nH}$, where n_H is the Hill coefficient.

Kinetic traces represent the data from one experiment only. All experiments were repeated on at least three oocytes. Reported kinetic parameters are the average from all experiments performed on that subtype. The data describing the time course of toxin inhibition were fit to an equation describing a simple exponential association of the form: $Y = (1-e^{-kt})$. The data describing the time course of recovery from toxin inhibition at low toxin concentrations were fit to an equation describing a simple exponential dissociation of the form: $Y = e^{-kt}$. The data describing the time course of recovery from toxin inhibition at high toxin concentrations were fit to an equation describing a complex exponential dissociation of the form: $Y = (1-(1-e^{-kt})^2)$.

EXAMPLE 8

Subtype specificity of MII

nAChR subunits expressed in *Xenopus* oocytes were used to quantitate the potency of MII at various nAChR combinations. Each subtype was inhibited in a dose-dependent manner by MII but with widely differing potencies (Fig. 9). α-conotoxin MII most potently inhibited the α3β2 combination with 200-fold to > 10,000-fold less potency at other subtypes (Table 2).

TABLE 2

Inhibition of nAChR Subtypes by Alpha-conotoxin MII

nAChR	IC_{50}	Hillslope
α3β2	4.9×10^{-10}	0.8
α7	1.3×10^{-7}	0.9
α4β2	4.3×10^{-7}	0.9
α2β2	9.8×10^{-7}	1.0
α3β4	1.1×10^{-6}	1.1
muscle	3.7×10^{-6}	0.7
α4β4	$>4.0 \times 10^{-6}$	N.D.
α2β4	$>4.0 \times 10^{-6}$	N.D

Many small molecules act as non-competitive inhibitors of nAChRs by blocking the open channel. Open channel block of nAChRs is generally dependent upon membrane potential. We examined whether MII block of the α3β2 nAChR was voltage-dependent. To accomplish this, acetylcholine response of α3β2 nAChRs to acetylcholine was measured over a range of membrane potentials both in the presence and absence of MII at its approximate IC_{50} (500 pM). As shown in Fig. 2, blockade by α-conotoxin MII shows no voltage dependence over the range tested (-100 mV to +10 mV).

To further examine the mechanism of action of MII, the differing off-rates of dihydro-β-erythroidine (DHβE) and α-conotoxin MII were utilized. DHβE has been shown to be a competitive antagonist of nAChRs. Blockade of α3β2 nAChRs expressed in oocytes by DHβE is fully reversed after four minutes of washout (Fig. 11A). In contrast, the α3β2 nAChR recovers relatively slowly from MII block after toxin washout (Fig. 11C). To test whether α-conotoxin MII was acting at the same site as DHβE, we pre-applied DHβE to α3β2 nAChRs. We then co-applied DHβE and α-conotoxin MII. If α-conotoxin MII and DHβE act at the same site, pre-application of the DHβE should protect the receptors from block by α-conotoxin MII. In this case, the recovery from block would follow the faster time course of block by DHβE alone. If preapplication of DhβE does not prevent the binding of α-conotoxin MII to the receptor, then the recovery from blockade by the co-applied DhβE and MII would be expected to follow the slower time course of block by α-conotoxin MII alone. As shown in Fig. 11B, the time course of recovery following washout of DHβE and α-

conotoxin MII is similar to that of washout of DHβE alone, indicating that DHβE prevents the binding of MII.

At low concentrations (e.g., near the IC_{50}) of α-conotoxin MII, recovery from block following toxin washout has a time course that is well fit by a single exponential decay function consistent with simple bi-molecular dissociation (Fig. 12). However, as the concentration of α-conotoxin MII approaches saturation, an initial lag in recovery after toxin washout occurs. This lag is maximal at fully saturated concentrations of α-conotoxin MII (data not shown). The time course of recovery from blockade with saturating concentrations MII is inconsistent with the simple bi-molecular dissociation (See dash lines in Fig. 13). Instead the time course is well fit by a model in which each receptor is assumed to have two binding sites which can either be occupied by ACh or α-conotoxin MII. Also in this model, occupation of either binding site by α-conotoxin MII is sufficient to block against induced opening of the receptor. Thus, at saturating concentrations, both binding sites are occupied by MII. Upon toxin washout each binding site becomes unoccupied following a time course of simple bi-molecular dissociation. Since both binding sites must be unoccupied by toxin for a receptor activation by agonist to occur, an initial lag in functional recovery following saturating toxin block is observed. The values of K_{off} calculated using this model under saturating toxin concentration matched those calculated under non-saturated condition validating the model. (Table 3).

TABLE 3

Equilibrium and Kinetic Constants of the Functional Block of nAChR by Variants of Class a A-Conotoxins

Peptide	Target	K_d (nM)	k_{off} (min^{-1})	k_{on} ($min^{-1}M^{-1}$)
MII	α3β2	0.33	0.13	400×10^6
	α3β4	2600	0.13	0.057×10^6
Chimera	α3β2	500	0.23	0.46×10^6
	α3β4	620	0.32	0.52×10^6
AuI	α3β2	>10,000	ND	ND
	α3β4	1500	0.33	0.23×10^6

EXAMPLE 9

Kinetics of Interaction with Receptor Subtypes

The affinity of a ligand is determined by its microscopic rates of association (k_{on}) and dissociation (k_{off}). As judged by measurements on voltage-clamped *Xenopus* oocytes expressing nAChRs, when MII blocks currents of α3β2 receptors, its on rate is relatively rapid ($k_{on} = 4 \times 10^8$ min^{-1} M^{-1}); its off rate is slow ($k_{off} = 0.13$ min^{-1}). This results in a high affinity interaction between α-conotoxin MII and α3β2 nAChRs. ($K_d = 3.3 \times 10^{-10}$ M). A substantially lower affinity is observed if either the α3 or β2 subunit is replaced with a different subunit. That is when the α3 subunit is switched to α4, the resulting α4β2 receptor is blocked by MII with a K_d that is 800-fold higher. If the β2 subunit is switched (to yield α3β4) an 8,000-fold decrease in MII potency is seen. Furthermore, when the k_{on} and k_{off} values of MII for these two types of receptors (a3b4 and α3β2) are measured, a most striking result is obtained. Despite a decrease of nearly 4-orders of magnitude in potency, when α-conotoxin blocks the α3β4 versus α3β2 receptor, k_{off} is changed little if any. Thus, the difference in potency is essentially accounted for by a corresponding decrease in toxin k_{on}.

Conversely, when the α subunit is changed (i.e., to yield α2β2 or α4β2 a marked increase in k_{off} for MII is found, the quantitation of which is presently beyond our assay capabilities). These results suggest that the k_{on} of the toxin is largely controlled by determinants on the β2 subunit whereas the α3 subunit may have the major determinants that control k_{off}.

EXAMPLE 10

Affinity of Chimera for α3/β2 Subtype

To further examine the kinetic interactions of toxin with receptor, a chimera of α-conotoxin MII was constructed. A series of peptides from the venom *Conus aulicus* was isolated that, unlike α-conotoxin MII, prefer the α3/β4 interface over that of the α3/β2. One of these peptides is α-conotoxin AuIA. The presence of either histidine or asparagine at position 12 is highly conserved in all conopeptides. A conserved sequence of each of the *aulicus* peptides was used in the design of the MII chimera indicated in Table 4 in which a string of four amino acids (9-12) of MII are replaced by FATN. In general, substitution of these four amino acids results in a change in selectivity and affinity for the nicotinic receptors. Compared to MII, the affinity of the chimera for the α3/β2 interface was more than 1,000-fold lower (K_d has changed from 330 pM for the wild-type to 500 nM for the chimera) but k_{off} was changed by a factor of less than two. Thus, the four amino

acid substitution does not affect toxin residues which determine off-rate (which must be elsewhere on the peptide), but clearly effects residues which determine on-rate. Other chimeras were synthesized in which amino acid fragment 9-12 was substituted from one peptide into another.

EXAMPLE 11

Cyclic Peptides Based on MII Motif

In order to test the significance of the HLEH fragment of MII (amino acid residues 9-12 of SEQ ID NO:1), several cyclic peptides based on this structure were constructed utilizing standard FMOC chemistry. These include: cyclic cys-HLEH-cys (SEQ ID NO:4), cyclic A-HLEH-A (SEQ ID NO:5) connected through an amide bond, and cyclic HLEH (amino acid residues 9-12 of SEQ ID NO:1) connected through an amide bond. These small peptides are screened for biological activity by the procedures of Example 8.

TABLE 4

Sequences of MII, AuI and a Chimera of the Two

Peptide	Sequence (ID NO:)
MII	GCCSNPVCHLEHSNLC* (1)
Chimera (MII HLEH[(9-12] FATN	GCCSNPVCFATNSNLC* (3)
AuI	GCCSYPPC**FATN**SGYC* (6)

The FATN sequence (amino acid residues 9-12 of SEQ ID NO:6) shown in bold is a conserved feature of at least three different α3β4-preferring α-conotoxins from *C. aulicus* venom.

EXAMPLE 12

Dock and Lock Model

Comparison of the data for interactions between MII and nAChRs (Examples 9 and 10) emerges as a two-step "dock and lock" mechanism to explain the remarkable subtype specificity of MII. The data suggest that two putative "faces" of the MII interacts with its respective binding sites on the receptor, and that the dual interaction may provide a general mechanism for the observed high receptor subtype specificity and affinity. Thus, it is proposed that α-conotoxin MII has two interaction surfaces, which are referred to as the "docking face" and the "locking face." The docking face interacts relatively rapidly with a site on the β2 subunit, which is referred to as the "docking

site." The second phase of toxin interaction involves a different surface of the toxin, the "locking face." This locking face binds to a site on the α3 subunit which is referred to as the "locking site." In the absence of docking interactions, the k_{on} for the "locking face- locking site" interaction may be quite slow. However, if the peptide is already docked (through the β2 docking site), the locking phase then proceeds much more rapidly (Figs 14A and 7B).

The data discussed above demonstrate that a switch in receptor subunits can cause a decrease in MII's affinity of several orders of magnitude, without affecting its k_{off} (implying that the locking site remains intact and that the change in affinity is primarily due to changes in docking interactions). The results with the FATN-αMII analog (Example 11; SEQ ID NO:3) and the kinetic results obtained with wild-type toxin acting on the α3β4 nicotinic receptor are thus suggestive that the docking face of the toxin is located on the hydrophilic side of the wedge and that this hydrophilic face interacts with a fast on-time with the β2 subunit. The other side of the wedge which is characterized by hydrophobic residues exposed to solvent, would be an attractive locus for the locking face of α-conotoxin MII, which is postulated to interact with high affinity on a site on the α3subunit of neuronal nicotinic receptor targets of this peptide. A cartoon representation of α-conotoxin MII interacting with the α3β2 and α3β4 receptors and of the FATN-α-conotoxin MII analog (SEQ ID NO:3) is shown in Fig. 14.

The presence of two distinct interaction faces, which lead to distinguishable docking-and-locking interactions as described herein may be a general design feature of many *Conus* peptides and may represent a novel paradigm for achieving subtype selective interaction with multisubunit receptors. The term "Janus-ligands" is suggested to refer to binding molecules that have two distinct interaction faces (from Janus, the two-faced Roman god of beginnings). α-Conotoxin MII would be a protype Janus ligand.

EXAMPLE 13

Synthesis of Organic Molecules as Ligands

The HLEH fragment of MII appears essential in determining activity and selectivity of the MII conopeptide. Computational examinations of the HLEH fragment are undertaken in order to develop an organic scaffold for use in developing small molecules. The spacial arrangement of the HLEH fragment is studied computationally using a vector analysis. Databases are then be searched to find organic fragments that have the proper spatial requirements and geometry to be used as a scaffold from which organic models are synthesized. The presence of two physically distinct

peptide surfaces (hydrophilic and hydrophobic) on the MII conopeptide and their interaction with α and β receptor subunits presents a specific strategy for designing ligands selective for receptors with different combinations of α and β subunits.

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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PCT Application No. WO 95/21193.
PCT Application No. WO 96/02286.
PCT Application No. WO 96/02646.
PCT Application No. WO 96/40871.
PCT Application No. WO 96/40959.
PCT Application No. WO 97/12635.
PCT Application No. WO 97/08300.

WHAT IS CLAIMED IS:

1. A substantially pure peptide having the general formula:

Xaa-Cys-Cys-Xaa-Xaa$_1$-Xaa$_2$-Xaa-Cys-Xaa$_3$-Xaa-Xaa$_4$-Xaa$_5$-Xaa-Xaa-Xaa-Cys,

wherein Xaa, Xaa$_1$, Xaa$_2$, Xaa$_3$ and Xaa$_4$ each is an amino acid selected from the group consisting of natural, modified or non-natural amino acids and Xaa$_5$ is His or Asn.

2. The peptide of claim 1 wherein the C-terminus is amidated.

3. The peptide of claim 1 wherein Xaa$_1$ is Asn or His.

4. The peptide of claim 1 wherein Xaa$_2$ is Pro or hydroxy-Pro.

5. The peptide of claim 1 wherein Xaa$_3$ is His.

6. The peptide of claim 1 wherein Xaa$_4$ is Glu.

7. The peptide of claim 1 wherein Xaa$_1$ is Asn or His and Xaa$_2$ is Pro or hydroxy-Pro.

8. The peptide of claim 7 wherein Xaa$_1$ is Asn.

9. The peptide of claim 7 wherein Xaa$_4$ is Glu and Xaa$_5$ is His.

10. The peptide of claim 7 wherein Xaa$_3$ is and Xaa$_4$ is Glu.

11. The peptide of claim 1 wherein the biological activity of the peptide is substantially the same as the biological activity of α-conotoxin MII.

12. The peptide of claim 7 wherein the biological activity of the peptide is substantially the same as the biological activity of α-conotoxin MII.

13. The peptide of claim 10 wherein the biological activity of the peptide is substantially the same as the biological activity of α-conotoxin MII.

14. A peptide analog, peptide mimetic or mimetic of α-conotoxin MII specific for one or more subtypes of neuronal nicotinic acetylcholine receptor (neuronal nAChR).

15. The peptide analog, peptide mimetic or mimetic of claim 14 wherein the specificity is for the α3β2 subtype of neuronal nAChR.

16. The peptide analog, peptide mimetic or mimetic of claim 14 wherein the specificity is for the α3β4 subtype of neuronal nAChR.

17. The peptide analog, peptide mimetic or mimetic of claim 14 wherein the specificity is for the α2β2 subtype of neuronal nAChR.

18. A method for screening compounds for neuronal nicotinic acetylcholine (nAChR) receptor antagonistic activity and receptor subtype which comprises determining the on and off rates for the binding of α-conotoxin MII and a compound to be screened to different subunits of nAChR and comparing said on and off rates.

19. The method of claim 18 wherein the subunits of nAChR are the α3β2 and α3β4 subunits.

20. A derivative, peptide analog, peptide mimetic or mimetic of α-conotoxin MII which selectively modulates biological activity at nAChRs.

21. A method for determining the three-dimensional structure of an alpha-conotoxin, analog which comprises:

(a) obtaining NMR spectroscopy data for the peptide;

(b) providing three-dimensional structural coordinates for a composition of MII; and

(c) determining the three-dimensional structure of the alpha-conotoxin by analyzing the data with reference to the previous structural coordinates using molecular replacement.

22. A method of claim 21 which further comprises testing a compound so identified for its ability to:

(a) bind to a neuronal nicitinic acetylcholine receptor (nAChR);

(b) inhibit the binding of a ligand to a neuronal nAChR; and/or

(c) inhibit a biological function mediated by a natural ligand of an nAChR.

23. A method for selecting a compound capable of binding to a neuronal nicotinic acetylcholine receptor (NAChR) which comprises:

(a) providing coordinates defining the three dimensional structure of MII or a portion thereof;

(b) characterizing points associated with that three dimensional structure with respect to the favorability of interactions with one or more selected functional groups;

(c) providing database of one or more dandidate compounds; and

(d) identifying from the database those compounds having structures which best fit the points of favorable interaction with the three dimensional structure.

24. A method of claim 23 which further comprises testing a compound so identified for its ability to:

(a) bind to neuronal nAChR,

(b) inhibit the binding of MII to a natural or non-natural ligand therefor, and/or

(c) inhibit a biological function mediated by MII.

25. A machine readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule comprising a MII peptide or a portion thereof.

26. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of an α-conotoxin or portion thereof based on the coordinates of Fig. 8, or based on coordinates having

a root mean square deviation therefrom with respect to conserved protein backbone atoms of not more than 1.5 Å.

27. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine-readable data which, when combined with a second set of machine-readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the coordinates corresponding to the second set of machine-readable data, wherein said first set of data comprises a Fourier transform of at least a portion of the coordinates according to Fig. 8; and said second set of data comprises coordinates of a molecule or molecular complex.

28. A method for displaying a three dimensional representation of a composition of MII which comprises:

a) providing a machine capable of reading data stored on a machine-readable storage medium of claim 25, programmed with instructions for using said data to display a graphical three-dimensional representation of a protein or protein ligand complex or portion thereof defined by said data, and loaded with a machine-readable storage medium of claim 25; and

b) permitting the machine to read said data and display the three-dimensional representation.

29. A method for designing a compound capable of binding to a neuronal nicotinic acetylcholine receptor (nAChR) which comprises:

(a) graphically displaying a three-dimensional representation based on coordinates defining the three-dimensional structure of MII or a portion thereof;

(b) characterizing the interactions between portions of a ligand that is known to bind to the protein to identify candidate moieties for replacement;

(c) providing a knowledge base of one or more candidate substitute moieties; and

(d) identifying from the knowledge base one or more substitute moieties which may be used to replace one or more selected portions of the ligand and retain at least a portion of the ligand's binding affinity for the protein.

30. The method of claim 29 which further comprises testing the compound for its modulating activity of said neuronal nAChR.

31. A method for designing a compound capable of binding to a neuronal nicotinic acetylcholine receptor (nAChR) which comprises:

(a) providing coordinates defining the three-dimensional structure of MII or a portion thereof;

(b) characterizing points associated with that three-dimensional structure to identify preferred points with respect to the favorability of interactions of one or more selected functional groups with the protein;

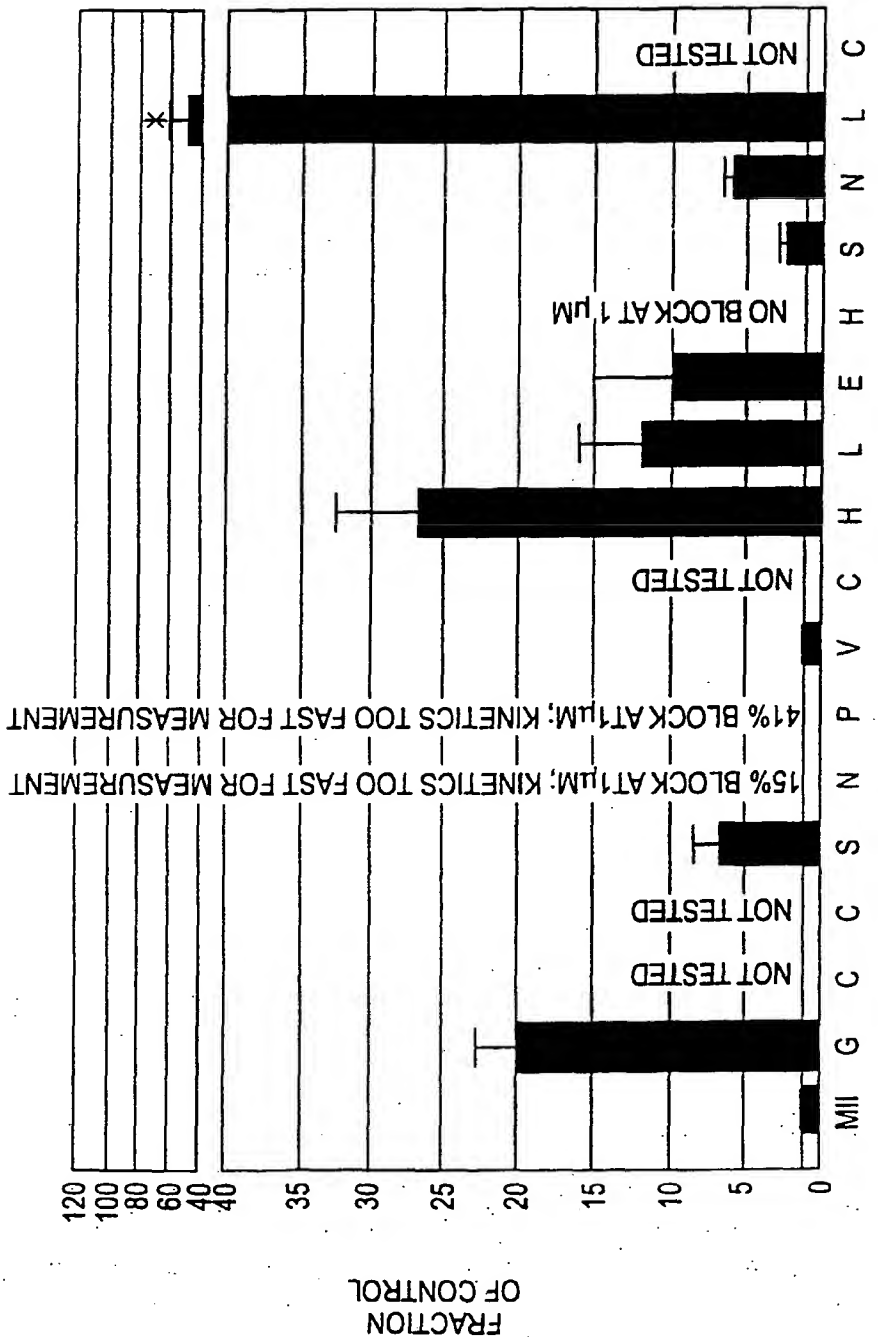
(c) characterizing one or more portions of a ligand that is known to bind to the protein that are proximal to the characterized points;

(d) providing a knowledge base of one or more molecular fragments or molecules;

(e) identifying from the knowledge base one or more fragments or molecules that permit connection of preferred points identified in (b) to portions of the ligand; and

(f) modifying the structure of the ligand by the covalent attachment thereto of one or more such fragments or molecules so identified in an orientation and location selected to permit the modified ligand to bind to the protein.

32. The method of claim 31 which further comprises testing the compound for its modulating activity of said neuronal nAChR.



*K ON, K OFF AND K_D ARE DIFFICULT TO DETERMINE ACCURATELY DUE TO FAST KINETICS OF TOXIN BLOCK.

FIG. 1

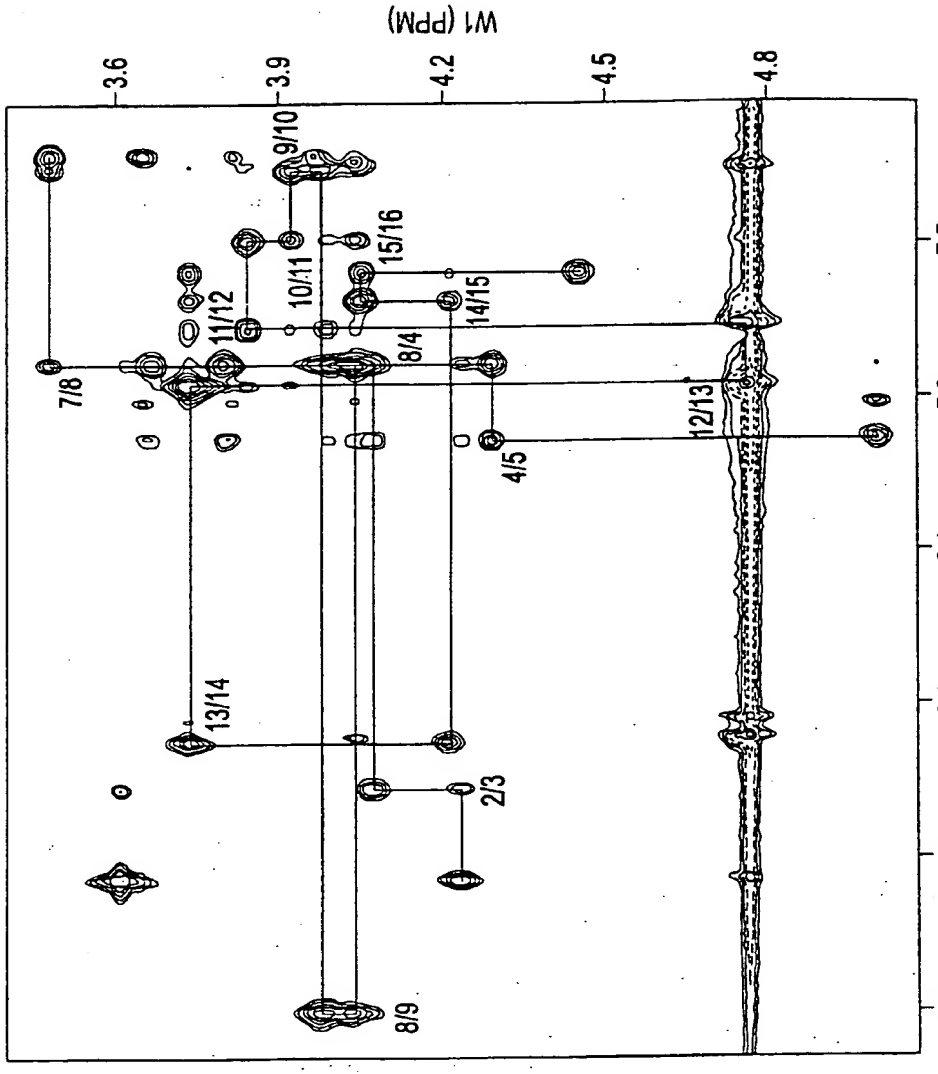

W1 (PPM)
3.6
3.9
4.2
4.5
4.8
9/10
15/16
10/11
14/15
11/12
8/4
7/8
12/13
4/5
13/14
2/3
8/9
7.5
7.8
8.1
8.4
8.7
9.0
W2 (PPM)

FIG. 2

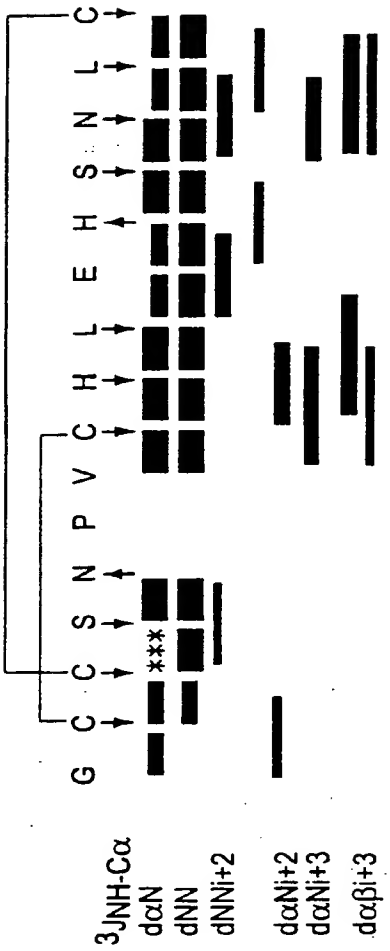

G C C S N P V C H L E H S N L C
***
$^3J_{NH-C\alpha}$
dαN
dNN
dNNi+2
dαNi+2
dαNi+3
dαβi+3

FIG. 3

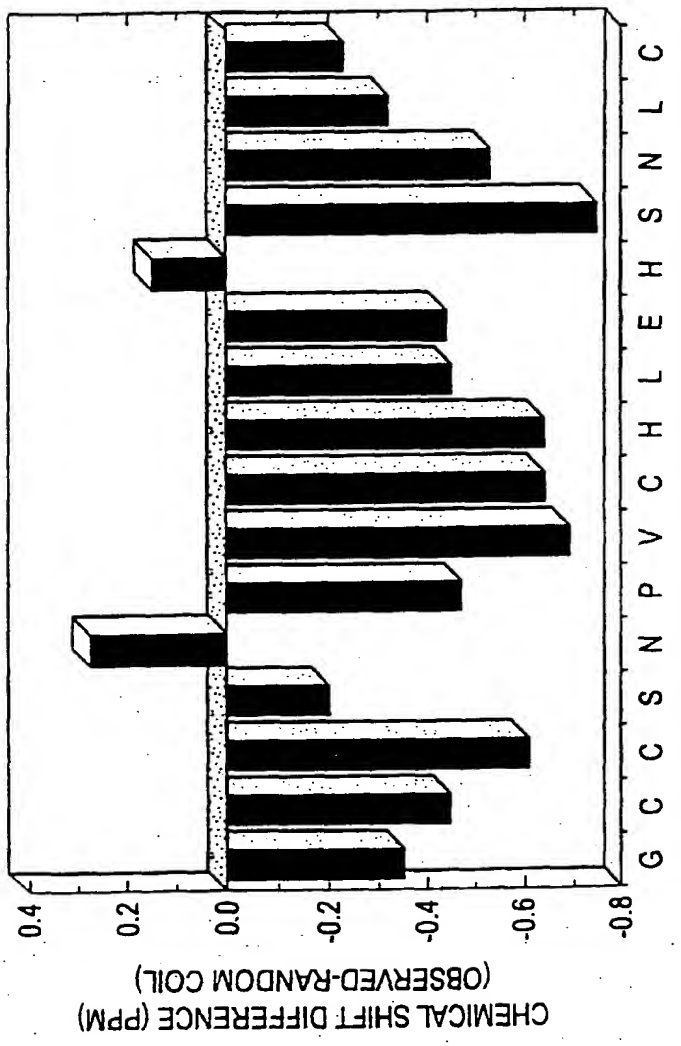

CHEMICAL SHIFT DIFFERENCE (PPM)
(OBSERVED-RANDOM COIL)
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
G C C S N P V C H L E H S N L C
RESIDUE

FIG. 4

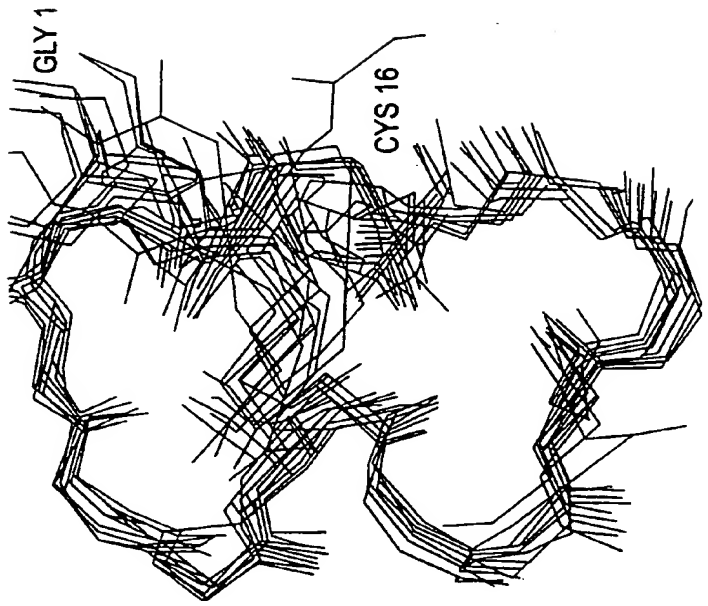


FIG. 5B

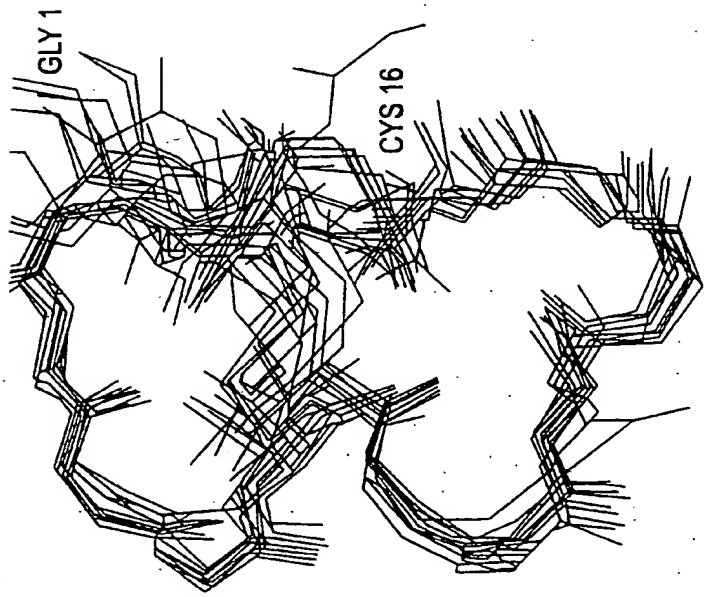


FIG. 5A

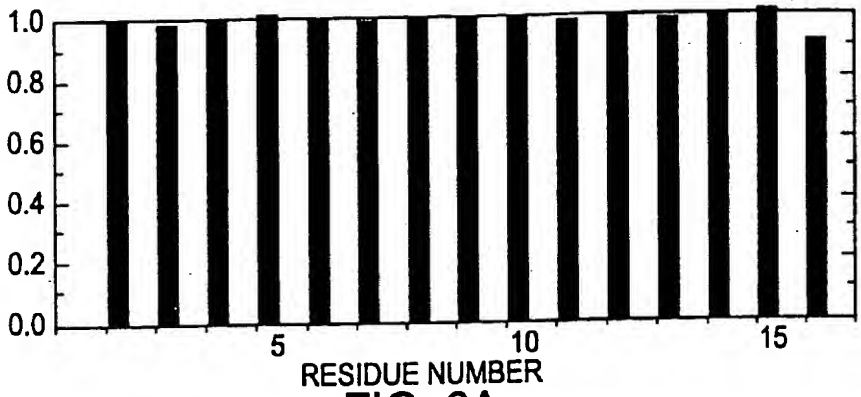


FIG. 6A

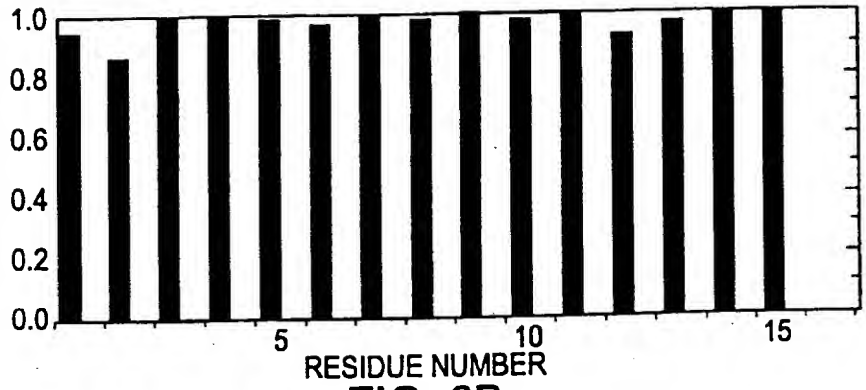


FIG. 6B

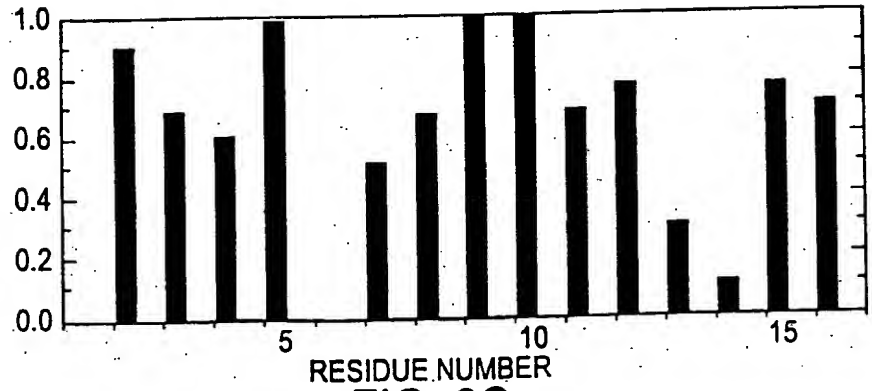


FIG. 6C

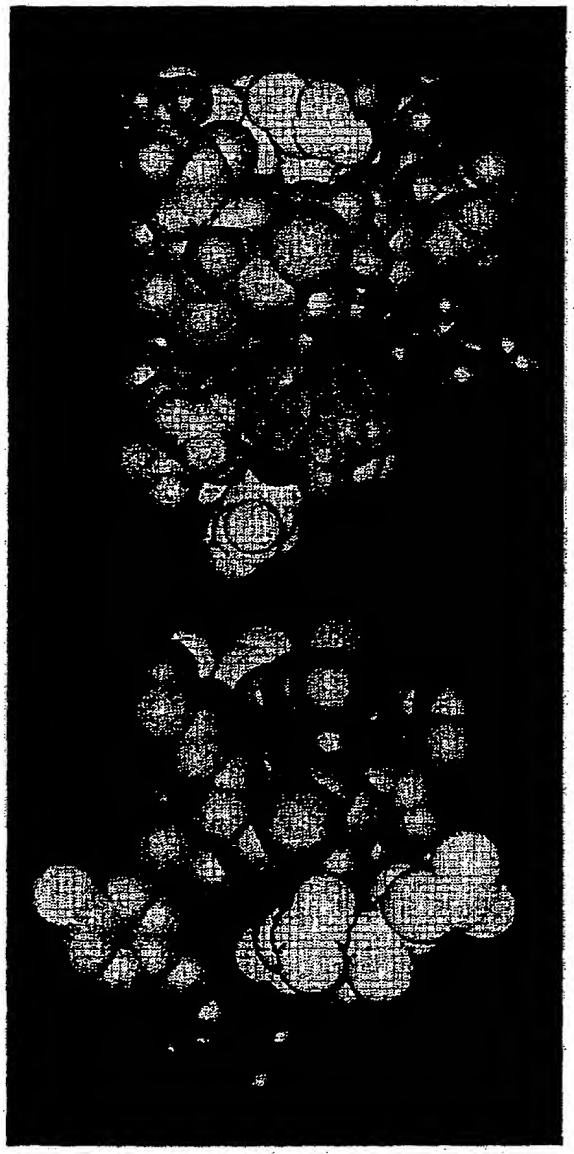


FIG. 7B

FIG. 7A

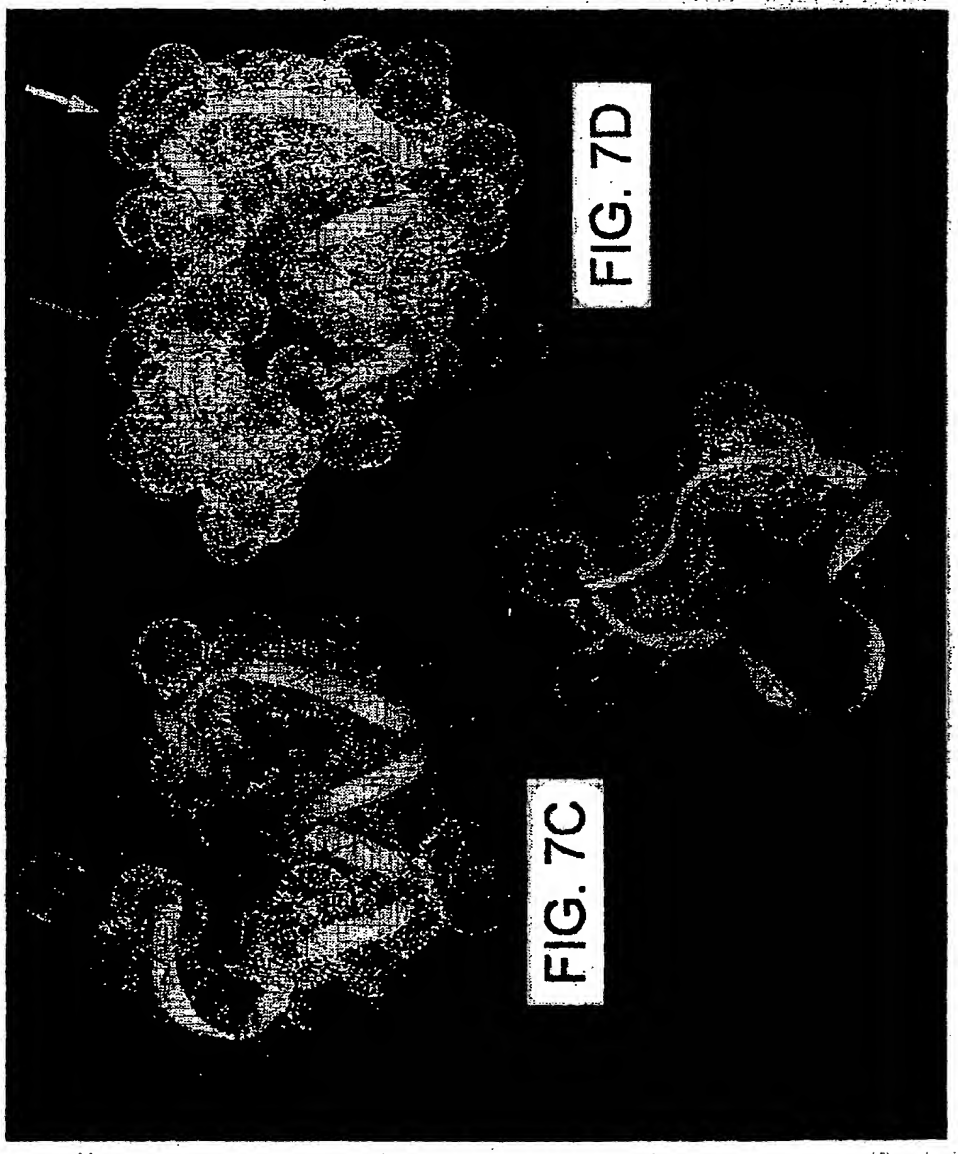


FIG. 7D
FIG. 7C
FIG. 7E

FIG. 8 - 1

```
ATOM      1  N   GLY     1      15.634  14.616 -13.035  0.00  0.00           N
ATOM      2  CA  GLY     1      16.374  15.823 -12.552  0.00  0.00           C
ATOM      3  C   GLY     1      16.601  16.957 -13.565  0.00  0.00           C
ATOM      4  O   GLY     1      16.407  16.772 -14.760  0.00  0.00           O
ATOM      5 1H   GLY     1      16.149  14.188 -13.818  1.00  0.00           H
ATOM      6 2H   GLY     1      15.549  13.935 -12.267  1.00  0.00           H
ATOM      7 3H   GLY     1      14.695  14.893 -13.353  1.00  0.00           H
ATOM      8 1HA  GLY     1      15.844  16.270 -11.694  0.00  0.00           H
ATOM      9 2HA  GLY     1      17.384  15.550 -12.193  0.00  0.00           H
ATOM     10  N   CYS     2      17.044  18.164 -13.217  0.00  0.00           N
ATOM     11  CA  CYS     2      17.260  18.675 -11.832  0.00  0.00           C
ATOM     12  C   CYS     2      15.966  19.090 -11.049  0.00  0.00           C
ATOM     13  O   CYS     2      15.593  18.382 -10.113  0.00  0.00           O
ATOM     14  CB  CYS     2      18.371  19.733 -11.934  0.00  0.00           C
ATOM     15  SG  CYS     2      19.281  19.941 -10.382  0.00  0.00           S
ATOM     16  H   CYS     2      17.281  18.712 -14.041  0.00  0.00           H
ATOM     17  HA  CYS     2      17.745  17.875 -11.249  0.00  0.00           H
ATOM     18 1HB  CYS     2      19.143  19.397 -12.649  0.00  0.00           H
ATOM     19 2HB  CYS     2      17.996  20.698 -12.322  0.00  0.00           H
ATOM     20  N   CYS     3      15.243  20.139 -11.483  0.00  0.00           N
ATOM     21  CA  CYS     3      13.872  20.523 -10.994  0.00  0.00           C
ATOM     22  C   CYS     3      12.795  19.383 -10.799  0.00  0.00           C
ATOM     23  O   CYS     3      11.986  19.455  -9.871  0.00  0.00           O
ATOM     24  CB  CYS     3      13.438  21.551 -12.071  0.00  0.00           C
ATOM     25  SG  CYS     3      11.902  22.446 -11.718  0.00  0.00           S
ATOM     26  H   CYS     3      15.586  20.503 -12.376  0.00  0.00           H
ATOM     27  HA  CYS     3      13.961  21.072 -10.017  0.00  0.00           H
ATOM     28 1HB  CYS     3      14.209  22.336 -12.216  0.00  0.00           H
ATOM     29 2HB  CYS     3      13.317  21.074 -13.063  0.00  0.00           H
ATOM     30  N   SER     4      12.820  18.327 -11.633  0.00  0.00           N
ATOM     31  CA  SER     4      11.986  17.111 -11.503  0.00  0.00           C
ATOM     32  C   SER     4      12.408  16.016 -10.457  0.00  0.00           C
ATOM     33  O   SER     4      11.576  15.193 -10.077  0.00  0.00           O
ATOM     34  CB  SER     4      11.936  16.580 -12.956  0.00  0.00           C
```

FIG. 8 - 2

```
ATOM   35  OG  SER   4      13.209  16.259 -13.539  0.00  0.00           O
ATOM   36  H   SER   4      13.571  18.289 -12.320  0.00  0.00           H
ATOM   37  HA  SER   4      10.956  17.405 -11.220  0.00  0.00           H
ATOM   38 1HB  SER   4      11.311  15.686 -12.964  0.00  0.00           H
ATOM   39 2HB  SER   4      11.395  17.301 -13.604  0.00  0.00           H
ATOM   40  HG  SER   4      13.078  16.330 -14.497  0.00  0.00           H
ATOM   41  N   ASN   5      13.648  16.019  -9.934  0.00  0.00           N
ATOM   42  CA  ASN   5      13.964  15.396  -8.631  0.00  0.00           C
ATOM   43  C   ASN   5      13.755  16.434  -7.481  0.00  0.00           C
ATOM   44  O   ASN   5      14.339  17.517  -7.578  0.00  0.00           O
ATOM   45  CB  ASN   5      15.467  15.027  -8.649  0.00  0.00           C
ATOM   46  CG  ASN   5      15.811  13.698  -9.280  0.00  0.00           C
ATOM   47  OD1 ASN   5      16.114  13.557 -10.457  0.00  0.00           O
ATOM   48  ND2 ASN   5      15.822  12.717  -8.434  0.00  0.00           N
ATOM   49  H   ASN   5      14.222  16.819 -10.206  0.00  0.00           H
ATOM   50  HA  ASN   5      13.348  14.497  -8.433  0.00  0.00           H
ATOM   51 1HB  ASN   5      16.100  15.832  -9.065  0.00  0.00           H
ATOM   52 2HB  ASN   5      15.814  14.978  -7.611  0.00  0.00           H
ATOM   53 1HD2 ASN   5      16.367  11.911  -8.732  0.00  0.00           H
ATOM   54 2HD2 ASN   5      15.707  13.088  -7.487  0.00  0.00           H
ATOM   55  N   PRO   6      13.055  16.153  -6.351  0.00  0.00           N
ATOM   56  CA  PRO   6      12.951  17.126  -5.223  0.00  0.00           C
ATOM   57  C   PRO   6      14.266  17.584  -4.506  0.00  0.00           C
ATOM   58  O   PRO   6      14.367  18.716  -4.040  0.00  0.00           O
ATOM   59  CB  PRO   6      11.867  16.477  -4.360  0.00  0.00           C
ATOM   60  CG  PRO   6      11.976  14.970  -4.613  0.00  0.00           C
ATOM   61  CD  PRO   6      12.445  14.838  -6.065  0.00  0.00           C
ATOM   62  HA  PRO   6      12.524  18.059  -5.584  0.00  0.00           H
ATOM   63 1HB  PRO   6      11.966  16.777  -3.306  0.00  0.00           H
ATOM   64 2HB  PRO   6      10.866  16.831  -4.679  0.00  0.00           H
ATOM   65 1HG  PRO   6      12.710  14.520  -3.924  0.00  0.00           H
ATOM   66 2HG  PRO   6      11.034  14.432  -4.417  0.00  0.00           H
ATOM   67 1HD  PRO   6      13.153  13.999  -6.168  0.00  0.00           H
ATOM   68 2HD  PRO   6      11.641  14.619  -6.788  0.00  0.00           H
```

FIG. 8 - 3

```
ATOM     69  N   VAL     7      15.297  16.745  -4.539  0.00  0.00      N
ATOM     70  CA  VAL     7      16.659  17.036  -4.017  0.00  0.00      C
ATOM     71  C   VAL     7      17.510  17.915  -4.975  0.00  0.00      C
ATOM     72  O   VAL     7      17.948  19.001  -4.584  0.00  0.00      O
ATOM     73  CB  VAL     7      17.269  15.639  -3.622  0.00  0.00      C
ATOM     74  CG1 VAL     7      18.794  15.639  -3.351  0.00  0.00      C
ATOM     75  CG2 VAL     7      16.615  15.033  -2.355  0.00  0.00      C
ATOM     76  H   VAL     7      15.093  15.928  -5.110  0.00  0.00      H
ATOM     77  HA  VAL     7      16.567  17.703  -3.149  0.00  0.00      H
ATOM     78  HB  VAL     7      17.068  14.940  -4.473  0.00  0.00      H
ATOM     79  1HG1 VAL   7      19.070  16.317  -2.520  0.00  0.00      H
ATOM     80  2HG1 VAL   7      19.171  14.633  -3.080  0.00  0.00      H
ATOM     81  3HG1 VAL   7      19.383  15.954  -4.233  0.00  0.00      H
ATOM     82  1HG2 VAL   7      15.520  14.920  -2.458  0.00  0.00      H
ATOM     83  2HG2 VAL   7      17.007  14.024  -2.120  0.00  0.00      H
ATOM     84  3HG2 VAL   7      16.784  15.658  -1.456  0.00  0.00      H
ATOM     85  N   CYS     8      17.723  17.496  -6.234  0.00  0.00      N
ATOM     86  CA  CYS     8      18.426  18.331  -7.241  0.00  0.00      C
ATOM     87  C   CYS     8      17.810  19.697  -7.633  0.00  0.00      C
ATOM     88  O   CYS     8      18.496  20.703  -7.829  0.00  0.00      O
ATOM     89  CB  CYS     8      18.832  17.434  -8.435  0.00  0.00      C
ATOM     90  SG  CYS     8      19.989  18.228  -9.590  0.00  0.00      S
ATOM     91  H   CYS     8      17.355  16.575  -6.422  0.00  0.00      H
ATOM     92  HA  CYS     8      19.259  18.670  -6.659  0.00  0.00      H
ATOM     93  1HB CYS     8      19.325  16.510  -8.074  0.00  0.00      H
ATOM     94  2HB CYS     8      17.940  17.112  -8.997  0.00  0.00      H
ATOM     95  N   HIS     9      16.490  19.730  -7.577  0.00  0.00      N
ATOM     96  CA  HIS     9      15.672  20.954  -7.520  0.00  0.00      C
ATOM     97  C   HIS     9      16.116  21.946  -6.408  0.00  0.00      C
ATOM     98  O   HIS     9      16.152  23.143  -6.649  0.00  0.00      O
ATOM     99  CB  HIS     9      14.212  20.441  -7.372  0.00  0.00      C
ATOM    100  CG  HIS     9      12.988  21.178  -6.837  0.00  0.00      C
ATOM    101  ND1 HIS     9      11.743  20.871  -7.343  0.00  0.00      N
ATOM    102  CD2 HIS     9      12.933  22.419  -6.207  0.00  0.00      C
```

FIG. 8 - 4

```
ATOM    103  CE1 HIS     9      11.061  22.027  -7.066  0.00  0.00      C
ATOM    104  NE2 HIS     9      11.665  22.970  -6.286  0.00  0.00      N
ATOM    105  H   HIS     9      16.122  18.799  -7.387  0.00  0.00      H
ATOM    106  HA  HIS     9      15.792  21.444  -8.470  0.00  0.00      H
ATOM    107  1HB HIS     9      13.964  19.804  -8.230  0.00  0.00      H
ATOM    108  2HB HIS     9      14.310  19.747  -6.514  0.00  0.00      H
ATOM    109  HD1 HIS     9      11.556  20.209  -8.116  0.00  0.00      H
ATOM    110  HD2 HIS     9      13.833  22.948  -5.987  0.00  0.00      H
ATOM    111  HE1 HIS     9      10.350  22.380  -7.807  0.00  0.00      H
ATOM    112  HE2 HIS     9      11.288  23.837  -5.876  1.00  0.00      H
ATOM    113  N   LEU    10      16.348  21.442  -5.199  0.00  0.00      N
ATOM    114  CA  LEU    10      16.543  22.306  -3.982  0.00  0.00      C
ATOM    115  C   LEU    10      18.003  22.749  -3.677  0.00  0.00      C
ATOM    116  O   LEU    10      18.247  23.915  -3.362  0.00  0.00      O
ATOM    117  CB  LEU    10      15.796  21.702  -2.764  0.00  0.00      C
ATOM    118  CG  LEU    10      14.248  21.705  -2.866  0.00  0.00      C
ATOM    119  CD1 LEU    10      13.632  20.894  -1.719  0.00  0.00      C
ATOM    120  CD2 LEU    10      13.634  23.120  -2.848  0.00  0.00      C
ATOM    121  H   LEU    10      16.639  20.446  -5.325  0.00  0.00      H
ATOM    122  HA  LEU    10      16.061  23.277  -4.172  0.00  0.00      H
ATOM    123  1HB LEU    10      16.160  20.668  -2.601  0.00  0.00      H
ATOM    124  2HB LEU    10      16.085  22.244  -1.841  0.00  0.00      H
ATOM    125  HG  LEU    10      13.977  21.199  -3.814  0.00  0.00      H
ATOM    126  1HD1 LEU   10      14.009  19.855  -1.706  0.00  0.00      H
ATOM    127  2HD1 LEU   10      13.853  21.334  -0.729  0.00  0.00      H
ATOM    128  3HD1 LEU   10      12.532  20.826  -1.811  0.00  0.00      H
ATOM    129  1HD2 LEU   10      13.884  23.667  -1.919  0.00  0.00      H
ATOM    130  2HD2 LEU   10      13.976  23.750  -3.687  0.00  0.00      H
ATOM    131  3HD2 LEU   10      12.530  23.089  -2.916  0.00  0.00      H
ATOM    132  N   GLU    11      18.974  21.867  -3.920  0.00  0.00      N
ATOM    133  CA  GLU    11      20.366  22.222  -4.268  0.00  0.00      C
ATOM    134  C   GLU    11      20.637  23.448  -5.202  0.00  0.00      C
ATOM    135  O   GLU    11      21.614  24.177  -5.020  0.00  0.00      O
ATOM    136  CB  GLU    11      20.855  20.906  -4.919  0.00  0.00      C
```

FIG. 8 - 5

```
ATOM    137  CG  GLU  11      21.268  19.744  -3.980  0.00  0.00      C
ATOM    138  CD  GLU  11      21.627  18.433  -4.686  0.00  0.00      C
ATOM    139  OE1 GLU  11      21.653  18.290  -5.906  0.00  0.00      O
ATOM    140  OE2 GLU  11      21.898  17.438  -3.795  0.00  0.00      O
ATOM    141  H   GLU  11      18.737  20.866  -3.861  1.00  0.00      H
ATOM    142  HA  GLU  11      20.934  22.422  -3.357  0.00  0.00      H
ATOM    143  1HB GLU  11      20.142  20.545  -5.688  0.00  0.00      H
ATOM    144  2HB GLU  11      21.713  21.169  -5.515  0.00  0.00      H
ATOM    145  1HG GLU  11      22.118  20.050  -3.342  0.00  0.00      H
ATOM    146  2HG GLU  11      20.433  19.538  -3.293  0.00  0.00      H
ATOM    147  HE2 GLU  11      22.110  16.618  -4.241  0.00  0.00      H
ATOM    148  N   HIS  12      19.798  23.633  -6.226  0.00  0.00      N
ATOM    149  CA  HIS  12      19.786  24.867  -7.040  0.00  0.00      C
ATOM    150  C   HIS  12      18.309  25.290  -7.270  0.00  0.00      C
ATOM    151  O   HIS  12      17.726  25.056  -8.328  0.00  0.00      O
ATOM    152  CB  HIS  12      20.582  24.609  -8.333  0.00  0.00      C
ATOM    153  CG  HIS  12      22.101  24.523  -8.182  0.00  0.00      C
ATOM    154  ND1 HIS  12      22.784  23.322  -8.090  0.00  0.00      N
ATOM    155  CD2 HIS  12      22.965  25.594  -7.876  0.00  0.00      C
ATOM    156  CE1 HIS  12      24.015  23.756  -7.667  0.00  0.00      C
ATOM    157  NE2 HIS  12      24.231  25.108  -7.557  0.00  0.00      N
ATOM    158  H   HIS  12      18.960  23.046  -6.147  0.00  0.00      H
ATOM    159  HA  HIS  12      20.270  25.707  -6.517  0.00  0.00      H
ATOM    160  1HB HIS  12      20.164  23.686  -8.773  0.00  0.00      H
ATOM    161  2HB HIS  12      20.351  25.426  -9.036  0.00  0.00      H
ATOM    162  HD1 HIS  12      22.391  22.375  -8.064  0.00  0.00      H
ATOM    163  HD2 HIS  12      22.639  26.626  -7.782  0.00  0.00      H
ATOM    164  HE1 HIS  12      24.768  23.040  -7.334  0.00  0.00      H
ATOM    165  HE2 HIS  12      25.090  25.620  -7.308  1.00  0.00      H
ATOM    166  N   SER  13      17.697  25.882  -6.236  0.00  0.00      N
ATOM    167  CA  SER  13      16.263  26.271  -6.249  0.00  0.00      C
ATOM    168  C   SER  13      15.832  27.466  -7.148  0.00  0.00      C
ATOM    169  O   SER  13      14.759  27.460  -7.748  0.00  0.00      O
ATOM    170  CB  SER  13      15.756  26.384  -4.793  0.00  0.00      C
```

FIG. 8 - 6

```
ATOM    171  OG  SER  13      14.332  26.272  -4.752  0.00  0.00           O
ATOM    172  H   SER  13      18.036  25.446  -5.395  0.00  0.00           H
ATOM    173  HA  SER  13      15.796  25.412  -6.707  0.00  0.00           H
ATOM    174 1HB  SER  13      16.191  25.599  -4.142  0.00  0.00           H
ATOM    175 2HB  SER  13      16.082  27.346  -4.346  0.00  0.00           H
ATOM    176  HG  SER  13      14.016  26.867  -4.059  0.00  0.00           H
ATOM    177  N   ASN  14      16.773  28.383  -7.341  0.00  0.00           N
ATOM    178  CA  ASN  14      16.901  29.190  -8.591  0.00  0.00           C
ATOM    179  C   ASN  14      16.718  28.475  -9.975  0.00  0.00           C
ATOM    180  O   ASN  14      16.103  29.023 -10.889  0.00  0.00           O
ATOM    181  CB  ASN  14      18.264  29.935  -8.516  0.00  0.00           C
ATOM    182  CG  ASN  14      19.577  29.139  -8.682  0.00  0.00           C
ATOM    183 OD1  ASN  14      19.814  28.095  -8.080  0.00  0.00           O
ATOM    184 ND2  ASN  14      20.472  29.600  -9.517  0.00  0.00           N
ATOM    185  H   ASN  14      17.588  27.967  -6.878  0.00  0.00           H
ATOM    186  HA  ASN  14      16.101  29.953  -8.559  0.00  0.00           H
ATOM    187 1HB  ASN  14      18.219  30.728  -9.282  0.00  0.00           H
ATOM    188 2HB  ASN  14      18.332  30.463  -7.551  0.00  0.00           H
ATOM    189 1HD2 ASN  14      21.324  29.044  -9.601  0.00  0.00           H
ATOM    190 2HD2 ASN  14      20.214  30.432 -10.057  0.00  0.00           H
ATOM    191  N   LEU  15      17.269  27.262 -10.102  0.00  0.00           N
ATOM    192  CA  LEU  15      17.117  26.420 -11.323  0.00  0.00           C
ATOM    193  C   LEU  15      15.850  25.494 -11.396  0.00  0.00           C
ATOM    194  O   LEU  15      15.600  24.903 -12.450  0.00  0.00           O
ATOM    195  CB  LEU  15      18.428  25.623 -11.576  0.00  0.00           C
ATOM    196  CG  LEU  15      19.755  26.418 -11.723  0.00  0.00           C
ATOM    197 CD1  LEU  15      20.920  25.447 -11.952  0.00  0.00           C
ATOM    198 CD2  LEU  15      19.730  27.443 -12.869  0.00  0.00           C
ATOM    199  H   LEU  15      17.588  26.893  -9.195  0.00  0.00           H
ATOM    200  HA  LEU  15      16.999  27.101 -12.177  0.00  0.00           H
ATOM    201 1HB  LEU  15      18.533  24.872 -10.772  0.00  0.00           H
ATOM    202 2HB  LEU  15      18.284  25.024 -12.497  0.00  0.00           H
ATOM    203  HG  LEU  15      19.943  26.970 -10.782  0.00  0.00           H
ATOM    204 1HD1 LEU  15      20.978  24.671 -11.170  0.00  0.00           H
```

FIG. 8 - 7

```
ATOM    205 2HD1 LEU    15      20.824  24.921 -12.921  0.00  0.00           H
ATOM    206 3HD1 LEU    15      21.890  25.977 -11.960  0.00  0.00           H
ATOM    207 1HD2 LEU    15      19.502  26.978 -13.847  0.00  0.00           H
ATOM    208 2HD2 LEU    15      18.970  28.229 -12.701  0.00  0.00           H
ATOM    209 3HD2 LEU    15      20.696  27.971 -12.978  0.00  0.00           H
ATOM    210  N   CYS    16      15.032  25.367 -10.333  0.00  0.00           N
ATOM    211  CA  CYS    16      13.605  24.985 -10.483  0.00  0.00           C
ATOM    212  C   CYS    16      12.591  26.176 -10.521  0.00  0.00           C
ATOM    213  O   CYS    16      11.707  26.224 -11.368  0.00  0.00           O
ATOM    214  CB  CYS    16      13.268  24.001  -9.358  0.00  0.00           C
ATOM    215  SG  CYS    16      11.802  23.053  -9.808  0.00  0.00           S
ATOM    216  H   CYS    16      15.380  25.854  -9.498  0.00  0.00           H
ATOM    217  HA  CYS    16      13.461  24.447 -11.437  0.00  0.00           H
ATOM    218 1HB CYS    16      14.020  23.224  -9.193  0.00  0.00           H
ATOM    219 2HB CYS    16      13.215  24.552  -8.399  0.00  0.00           H
TER     220     CYS    16
HETATM  221  N   NH2   17H     12.608  27.130  -9.608  0.00  0.00           N
HETATM  222 1HN NH2   17H     13.333  27.130  -8.876  1.00  0.00           H
HETATM  223 2HN NH2   17H     11.896  27.874  -9.628  1.00  0.00           H
ENDMDL
MODEL        2
ATOM    224  N   GLY     1      14.267  17.154 -16.168  0.00  0.00           N
ATOM    225  CA  GLY     1      15.718  17.213 -15.794  0.00  0.00           C
ATOM    226  C   GLY     1      15.977  17.230 -14.264  0.00  0.00           C
ATOM    227  O   GLY     1      15.276  16.529 -13.537  0.00  0.00           O
ATOM    228 1H  GLY     1      13.780  17.978 -15.788  1.00  0.00           H
ATOM    229 2H  GLY     1      14.176  17.146 -17.194  1.00  0.00           H
ATOM    230 3H  GLY     1      13.846  16.297 -15.781  1.00  0.00           H
ATOM    231 1HA GLY     1      16.245  16.323 -16.195  0.00  0.00           H
ATOM    232 2HA GLY     1      16.206  18.082 -16.280  0.00  0.00           H
ATOM    233  N   CYS     2      16.947  17.998 -13.736  0.00  0.00           N
ATOM    234  CA  CYS     2      17.280  17.912 -12.279  0.00  0.00           C
ATOM    235  C   CYS     2      16.307  18.759 -11.354  0.00  0.00           C
ATOM    236  O   CYS     2      15.915  18.300 -10.283  0.00  0.00           O
```

FIG. 8 - 8

```
ATOM   237  CB  CYS     2      18.750  18.346 -12.154  0.00  0.00           C
ATOM   238  SG  CYS     2      19.069  18.878 -10.463  0.00  0.00           S
ATOM   239  H   CYS     2      17.697  18.283 -14.376  0.00  0.00           H
ATOM   240  HA  CYS     2      17.217  16.863 -11.923  0.00  0.00           H
ATOM   241 1HB  CYS     2      19.444  17.562 -12.506  0.00  0.00           H
ATOM   242 2HB  CYS     2      18.928  19.245 -12.774  0.00  0.00           H
ATOM   243  N   CYS     3      15.877  19.965 -11.766  0.00  0.00           N
ATOM   244  CA  CYS     3      14.608  20.610 -11.289  0.00  0.00           C
ATOM   245  C   CYS     3      13.303  19.715 -11.225  0.00  0.00           C
ATOM   246  O   CYS     3      12.479  19.936 -10.337  0.00  0.00           O
ATOM   247  CB  CYS     3      14.460  21.831 -12.226  0.00  0.00           C
ATOM   248  SG  CYS     3      12.912  22.710 -11.945  0.00  0.00           S
ATOM   249  H   CYS     3      16.327  20.233 -12.647  0.00  0.00           H
ATOM   250  HA  CYS     3      14.740  21.021 -10.252  0.00  0.00           H
ATOM   251 1HB  CYS     3      15.285  22.556 -12.082  0.00  0.00           H
ATOM   252 2HB  CYS     3      14.477  21.547 -13.296  0.00  0.00           H
ATOM   253  N   SER     4      13.123  18.690 -12.085  0.00  0.00           N
ATOM   254  CA  SER     4      12.080  17.647 -11.888  0.00  0.00           C
ATOM   255  C   SER     4      12.391  16.468 -10.886  0.00  0.00           C
ATOM   256  O   SER     4      11.554  15.583 -10.718  0.00  0.00           O
ATOM   257  CB  SER     4      11.690  17.171 -13.307  0.00  0.00           C
ATOM   258  OG  SER     4      12.630  16.273 -13.903  0.00  0.00           O
ATOM   259  H   SER     4      13.953  18.411 -12.605  0.00  0.00           H
ATOM   260  HA  SER     4      11.170  18.126 -11.471  0.00  0.00           H
ATOM   261 1HB  SER     4      10.731  16.655 -13.216  0.00  0.00           H
ATOM   262 2HB  SER     4      11.478  18.024 -13.982  0.00  0.00           H
ATOM   263  HG  SER     4      12.671  15.500 -13.317  0.00  0.00           H
ATOM   264  N   ASN     5      13.518  16.484 -10.152  0.00  0.00           N
ATOM   265  CA  ASN     5      13.727  15.715  -8.918  0.00  0.00           C
ATOM   266  C   ASN     5      13.257  16.443  -7.608  0.00  0.00           C
ATOM   267  O   ASN     5      13.005  17.652  -7.625  0.00  0.00           O
ATOM   268  CB  ASN     5      15.248  15.453  -8.868  0.00  0.00           C
ATOM   269  CG  ASN     5      15.815  14.162  -9.386  0.00  0.00           C
ATOM   270  OD1 ASN     5      15.531  13.678 -10.472  0.00  0.00           O
```

FIG. 8-9

```
ATOM    271  ND2 ASN     5      16.768  13.664  -8.665  0.00  0.00           N
ATOM    272  H   ASN     5      14.288  17.138 -10.338  0.00  0.00           H
ATOM    273  HA  ASN     5      13.260  14.728  -8.976  0.00  0.00           H
ATOM    274  1HB ASN     5      15.763  16.040  -9.603  0.00  0.00           H
ATOM    275  2HB ASN     5      15.710  15.930  -8.009  0.00  0.00           H
ATOM    276  1HD2 ASN    5      17.365  13.107  -9.271  0.00  0.00           H
ATOM    277  2HD2 ASN    5      17.030  14.217  -7.846  0.00  0.00           H
ATOM    278  N   PRO     6      13.219  15.766  -6.432  0.00  0.00           N
ATOM    279  CA  PRO     6      13.046  16.445  -5.115  0.00  0.00           C
ATOM    280  C   PRO     6      14.257  17.306  -4.627  0.00  0.00           C
ATOM    281  O   PRO     6      14.159  18.505  -4.368  0.00  0.00           O
ATOM    282  CB  PRO     6      12.647  15.247  -4.238  0.00  0.00           C
ATOM    283  CG  PRO     6      13.429  14.074  -4.834  0.00  0.00           C
ATOM    284  CD  PRO     6      13.367  14.298  -6.333  0.00  0.00           C
ATOM    285  HA  PRO     6      12.197  17.119  -5.110  0.00  0.00           H
ATOM    286  1HB PRO     6      12.850  15.433  -3.173  0.00  0.00           H
ATOM    287  2HB PRO     6      11.557  15.056  -4.313  0.00  0.00           H
ATOM    288  1HG PRO     6      14.474  14.066  -4.483  0.00  0.00           H
ATOM    289  2HG PRO     6      13.061  13.093  -4.561  0.00  0.00           H
ATOM    290  1HD PRO     6      14.278  13.884  -6.779  0.00  0.00           H
ATOM    291  2HD PRO     6      12.540  13.796  -6.867  0.00  0.00           H
ATOM    292  N   VAL     7      15.412  16.657  -4.561  0.00  0.00           N
ATOM    293  CA  VAL     7      16.610  17.124  -3.820  0.00  0.00           C
ATOM    294  C   VAL     7      17.524  18.017  -4.681  0.00  0.00           C
ATOM    295  O   VAL     7      17.855  19.138  -4.293  0.00  0.00           O
ATOM    296  CB  VAL     7      17.305  15.801  -3.328  0.00  0.00           C
ATOM    297  CG1 VAL     7      18.715  15.985  -2.741  0.00  0.00           C
ATOM    298  CG2 VAL     7      16.502  15.043  -2.257  0.00  0.00           C
ATOM    299  H   VAL     7      15.273  15.661  -4.749  0.00  0.00           H
ATOM    300  HA  VAL     7      16.319  17.791  -2.987  0.00  0.00           H
ATOM    301  HB  VAL     7      17.399  15.124  -4.210  0.00  0.00           H
ATOM    302  1HG1 VAL    7      18.703  16.661  -1.865  0.00  0.00           H
ATOM    303  2HG1 VAL    7      19.150  15.022  -2.417  0.00  0.00           H
ATOM    304  3HG1 VAL    7      19.416  16.412  -3.481  0.00  0.00           H
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FIG. 8-10

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ATOM    305 1HG2 VAL     7      15.476  14.815  -2.595  0.00  0.00      H
ATOM    306 2HG2 VAL     7      16.976  14.076  -2.011  0.00  0.00      H
ATOM    307 3HG2 VAL     7      16.415  15.634  -1.328  0.00  0.00      H
ATOM    308  N   CYS     8      17.945  17.519  -5.852  0.00  0.00      N
ATOM    309  CA  CYS     8      18.800  18.310  -6.774  0.00  0.00      C
ATOM    310  C   CYS     8      18.200  19.595  -7.433  0.00  0.00      C
ATOM    311  O   CYS     8      18.901  20.560  -7.755  0.00  0.00      O
ATOM    312  CB  CYS     8      19.585  17.408  -7.744  0.00  0.00      C
ATOM    313  SG  CYS     8      18.676  17.283  -9.293  0.00  0.00      S
ATOM    314  H   CYS     8      17.652  16.545  -5.925  0.00  0.00      H
ATOM    315  HA  CYS     8      19.478  18.741  -6.057  0.00  0.00      H
ATOM    316 1HB  CYS     8      20.579  17.844  -7.956  0.00  0.00      H
ATOM    317 2HB  CYS     8      19.785  16.400  -7.330  0.00  0.00      H
ATOM    318  N   HIS     9      16.872  19.603  -7.516  0.00  0.00      N
ATOM    319  CA  HIS     9      16.022  20.810  -7.579  0.00  0.00      C
ATOM    320  C   HIS     9      16.327  21.879  -6.487  0.00  0.00      C
ATOM    321  O   HIS     9      16.337  23.069  -6.777  0.00  0.00      O
ATOM    322  CB  HIS     9      14.563  20.257  -7.547  0.00  0.00      C
ATOM    323  CG  HIS     9      13.278  20.974  -7.119  0.00  0.00      C
ATOM    324  ND1 HIS     9      12.032  20.482  -7.452  0.00  0.00      N
ATOM    325  CD2 HIS     9      13.125  22.225  -6.531  0.00  0.00      C
ATOM    326  CE1 HIS     9      11.216  21.519  -7.082  0.00  0.00      C
ATOM    327  NE2 HIS     9      11.787  22.598  -6.466  0.00  0.00      N
ATOM    328  H   HIS     9      16.502  18.717  -7.185  0.00  0.00      H
ATOM    329  HA  HIS     9      16.215  21.262  -8.533  0.00  0.00      H
ATOM    330 1HB  HIS     9      14.396  19.611  -8.422  0.00  0.00      H
ATOM    331 2HB  HIS     9      14.586  19.572  -6.681  0.00  0.00      H
ATOM    332  HD1 HIS     9      11.832  19.638  -8.011  0.00  0.00      H
ATOM    333  HD2 HIS     9      13.978  22.826  -6.296  0.00  0.00      H
ATOM    334  HE1 HIS     9      10.181  21.570  -7.416  0.00  0.00      H
ATOM    335  HE2 HIS     9      11.353  23.443  -6.068  1.00  0.00      H
ATOM    336  N   LEU    10      16.461  21.442  -5.238  0.00  0.00      N
ATOM    337  CA  LEU    10      16.551  22.359  -4.048  0.00  0.00      C
ATOM    338  C   LEU    10      17.980  22.858  -3.652  0.00  0.00      C
```

FIG. 8 - 11

ATOM	339	O	LEU	10	18.166	24.025	-3.307	0.00	0.00	O
ATOM	340	CB	LEU	10	15.731	21.762	-2.874	0.00	0.00	C
ATOM	341	CG	LEU	10	14.193	21.697	-3.089	0.00	0.00	C
ATOM	342	CD1	LEU	10	13.532	20.881	-1.974	0.00	0.00	C
ATOM	343	CD2	LEU	10	13.533	23.090	-3.152	0.00	0.00	C
ATOM	344	H	LEU	10	16.686	20.422	-5.257	0.00	0.00	H
ATOM	345	HA	LEU	10	16.057	23.307	-4.309	0.00	0.00	H
ATOM	346	1HB	LEU	10	16.122	20.751	-2.645	0.00	0.00	H
ATOM	347	2HB	LEU	10	15.929	22.343	-1.952	0.00	0.00	H
ATOM	348	HG	LEU	10	13.986	21.158	-4.033	0.00	0.00	H
ATOM	349	1HD1	LEU	10	13.933	19.852	-1.936	0.00	0.00	H
ATOM	350	2HD1	LEU	10	13.681	21.334	-0.976	0.00	0.00	H
ATOM	351	3HD1	LEU	10	12.441	20.783	-2.133	0.00	0.00	H
ATOM	352	1HD2	LEU	10	13.703	23.671	-2.225	0.00	0.00	H
ATOM	353	2HD2	LEU	10	13.910	23.708	-3.986	0.00	0.00	H
ATOM	354	3HD2	LEU	10	12.438	23.019	-3.290	0.00	0.00	H
ATOM	355	N	GLU	11	19.005	22.036	-3.865	0.00	0.00	N
ATOM	356	CA	GLU	11	20.372	22.479	-4.230	0.00	0.00	C
ATOM	357	C	GLU	11	20.553	23.589	-5.329	0.00	0.00	C
ATOM	358	O	GLU	11	21.516	24.355	-5.322	0.00	0.00	O
ATOM	359	CB	GLU	11	20.965	21.149	-4.750	0.00	0.00	C
ATOM	360	CG	GLU	11	21.455	20.100	-3.724	0.00	0.00	C
ATOM	361	CD	GLU	11	22.052	18.829	-4.335	0.00	0.00	C
ATOM	362	OE1	GLU	11	22.158	18.618	-5.542	0.00	0.00	O
ATOM	363	OE2	GLU	11	22.453	17.953	-3.377	0.00	0.00	O
ATOM	364	H	GLU	11	18.838	21.024	-3.769	1.00	0.00	H
ATOM	365	HA	GLU	11	20.916	22.823	-3.343	0.00	0.00	H
ATOM	366	1HB	GLU	11	20.300	20.674	-5.496	0.00	0.00	H
ATOM	367	2HB	GLU	11	21.806	21.427	-5.359	0.00	0.00	H
ATOM	368	1HG	GLU	11	22.204	20.543	-3.042	0.00	0.00	H
ATOM	369	2HG	GLU	11	20.611	19.803	-3.084	0.00	0.00	H
ATOM	370	HE2	GLU	11	22.820	17.169	-3.788	0.00	0.00	H
ATOM	371	N	HIS	12	19.668	23.583	-6.329	0.00	0.00	N
ATOM	372	CA	HIS	12	19.632	24.590	-7.415	0.00	0.00	C

FIG. 8 - 12

ATOM	373	C	HIS	12	18.228	25.279	-7.467	0.00	0.00	C
ATOM	374	O	HIS	12	17.504	25.191	-8.458	0.00	0.00	O
ATOM	375	CB	HIS	12	20.050	23.866	-8.721	0.00	0.00	C
ATOM	376	CG	HIS	12	21.465	23.272	-8.765	0.00	0.00	C
ATOM	377	ND1	HIS	12	21.705	21.925	-8.557	0.00	0.00	N
ATOM	378	CD2	HIS	12	22.683	23.982	-8.781	0.00	0.00	C
ATOM	379	CE1	HIS	12	23.072	21.918	-8.425	0.00	0.00	C
ATOM	380	NE2	HIS	12	23.746	23.104	-8.581	0.00	0.00	N
ATOM	381	H	HIS	12	18.854	23.028	-6.071	0.00	0.00	H
ATOM	382	HA	HIS	12	20.356	25.393	-7.231	0.00	0.00	H
ATOM	383	1HB	HIS	12	19.305	23.072	-8.900	0.00	0.00	H
ATOM	384	2HB	HIS	12	19.922	24.566	-9.561	0.00	0.00	H
ATOM	385	HD1	HIS	12	21.013	21.211	-8.287	0.00	0.00	H
ATOM	386	HD2	HIS	12	22.761	25.064	-8.831	0.00	0.00	H
ATOM	387	HE1	HIS	12	23.605	21.006	-8.146	0.00	0.00	H
ATOM	388	HE2	HIS	12	24.759	23.292	-8.556	1.00	0.00	H
ATOM	389	N	SER	13	17.836	25.928	-6.362	0.00	0.00	N
ATOM	390	CA	SER	13	16.441	26.361	-6.091	0.00	0.00	C
ATOM	391	C	SER	13	15.868	27.547	-6.898	0.00	0.00	C
ATOM	392	O	SER	13	14.771	27.472	-7.441	0.00	0.00	O
ATOM	393	CB	SER	13	16.240	26.544	-4.566	0.00	0.00	C
ATOM	394	OG	SER	13	17.091	27.570	-4.045	0.00	0.00	O
ATOM	395	H	SER	13	18.337	25.569	-5.566	0.00	0.00	H
ATOM	396	HA	SER	13	15.859	25.510	-6.412	0.00	0.00	H
ATOM	397	1HB	SER	13	15.182	26.797	-4.347	0.00	0.00	H
ATOM	398	2HB	SER	13	16.425	25.600	-4.025	0.00	0.00	H
ATOM	399	HG	SER	13	16.898	27.680	-3.106	0.00	0.00	H
ATOM	400	N	ASN	14	16.711	28.553	-7.058	0.00	0.00	N
ATOM	401	CA	ASN	14	16.737	29.460	-8.249	0.00	0.00	C
ATOM	402	C	ASN	14	16.410	28.835	-9.656	0.00	0.00	C
ATOM	403	O	ASN	14	15.664	29.413	-10.445	0.00	0.00	O
ATOM	404	CB	ASN	14	18.130	30.154	-8.143	0.00	0.00	C
ATOM	405	CG	ASN	14	18.511	31.133	-9.251	0.00	0.00	C
ATOM	406	OD1	ASN	14	18.145	32.298	-9.248	0.00	0.00	O

FIG. 8 - 13

```
ATOM    407  ND2 ASN  14      19.273  30.693 -10.222  0.00  0.00           N
ATOM    408  H   ASN  14      17.533  28.211  -6.552  0.00  0.00           H
ATOM    409  HA  ASN  14      15.958  30.222  -8.103  0.00  0.00           H
ATOM    410 1HB  ASN  14      18.169  30.739  -7.203  0.00  0.00           H
ATOM    411 2HB  ASN  14      18.940  29.408  -8.032  0.00  0.00           H
ATOM    412 1HD2 ASN  14      19.438  31.380 -10.959  0.00  0.00           H
ATOM    413 2HD2 ASN  14      19.395  29.682 -10.278  0.00  0.00           H
ATOM    414  N   LEU  15      16.962  27.653  -9.949  0.00  0.00           N
ATOM    415  CA  LEU  15      16.741  26.927 -11.229  0.00  0.00           C
ATOM    416  C   LEU  15      15.509  25.946 -11.288  0.00  0.00           C
ATOM    417  O   LEU  15      15.205  25.390 -12.345  0.00  0.00           O
ATOM    418  CB  LEU  15      18.105  26.267 -11.585  0.00  0.00           C
ATOM    419  CG  LEU  15      19.301  27.263 -11.704  0.00  0.00           C
ATOM    420  CD1 LEU  15      20.233  27.331 -10.482  0.00  0.00           C
ATOM    421  CD2 LEU  15      20.137  26.987 -12.949  0.00  0.00           C
ATOM    422  H   LEU  15      17.505  27.222  -9.199  0.00  0.00           H
ATOM    423  HA  LEU  15      16.537  27.672 -12.014  0.00  0.00           H
ATOM    424 1HB  LEU  15      18.333  25.449 -10.882  0.00  0.00           H
ATOM    425 2HB  LEU  15      17.954  25.747 -12.552  0.00  0.00           H
ATOM    426  HG  LEU  15      18.858  28.275 -11.796  0.00  0.00           H
ATOM    427 1HD1 LEU  15      19.680  27.495  -9.541  0.00  0.00           H
ATOM    428 2HD1 LEU  15      20.851  26.426 -10.371  0.00  0.00           H
ATOM    429 3HD1 LEU  15      20.936  28.183 -10.576  0.00  0.00           H
ATOM    430 1HD2 LEU  15      19.510  27.042 -13.859  0.00  0.00           H
ATOM    431 2HD2 LEU  15      20.941  27.736 -13.066  0.00  0.00           H
ATOM    432 3HD2 LEU  15      20.599  25.985 -12.915  0.00  0.00           H
ATOM    433  N   CYS  16      14.777  25.764 -10.178  0.00  0.00           N
ATOM    434  CA  CYS  16      13.314  25.476 -10.211  0.00  0.00           C
ATOM    435  C   CYS  16      12.402  26.741 -10.052  0.00  0.00           C
ATOM    436  O   CYS  16      11.558  27.025 -10.893  0.00  0.00           O
ATOM    437  CB  CYS  16      13.014  24.354  -9.201  0.00  0.00           C
ATOM    438  SG  CYS  16      12.506  22.810  -9.987  0.00  0.00           S
ATOM    439  H   CYS  16      15.221  26.270  -9.398  0.00  0.00           H
ATOM    440  HA  CYS  16      13.008  25.068 -11.181  0.00  0.00           H
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FIG. 8 - 14

```
ATOM    441  1HB  CYS      16      13.838  24.189  -8.482  0.00  0.00           H
ATOM    442  2HB  CYS      16      12.139  24.641  -8.605  0.00  0.00           H
TER     443       CYS      16
HETATM  444  N    NH2     17H      12.467  27.507  -8.982  0.00  0.00           N
HETATM  445  1HN  NH2     17H      11.921  28.368  -9.091  0.00  0.00           H
HETATM  446  2HN  NH2     17H      13.302  27.373  -8.381  0.00  0.00           H
ENDMDL
MODEL        3
ATOM    447  N    GLY      1       14.339  14.763  -15.648  0.00  0.00           N
ATOM    448  CA   GLY      1       15.501  15.674  -15.380  0.00  0.00           C
ATOM    449  C    GLY      1       15.797  15.944  -13.877  0.00  0.00           C
ATOM    450  O    GLY      1       15.122  15.395  -13.008  0.00  0.00           O
ATOM    451  1H   GLY      1       14.514  13.846  -15.214  1.00  0.00           H
ATOM    452  2H   GLY      1       13.482  15.173  -15.250  1.00  0.00           H
ATOM    453  3H   GLY      1       14.223  14.645  -16.665  1.00  0.00           H
ATOM    454  1HA  GLY      1       16.418  15.264  -15.850  0.00  0.00           H
ATOM    455  2HA  GLY      1       15.328  16.651  -15.876  0.00  0.00           H
ATOM    456  N    CYS      2       16.776  16.803  -13.541  0.00  0.00           N
ATOM    457  CA   CYS      2       17.170  17.004  -12.112  0.00  0.00           C
ATOM    458  C    CYS      2       16.202  17.965  -11.305  0.00  0.00           C
ATOM    459  O    CYS      2       15.843  17.666  -10.165  0.00  0.00           O
ATOM    460  CB   CYS      2       18.629  17.503  -12.156  0.00  0.00           C
ATOM    461  SG   CYS      2       19.008  18.386  -10.634  0.00  0.00           S
ATOM    462  H    CYS      2       17.487  16.987  -14.258  0.00  0.00           H
ATOM    463  HA   CYS      2       17.172  16.036  -11.572  0.00  0.00           H
ATOM    464  1HB  CYS      2       19.337  16.682  -12.370  0.00  0.00           H
ATOM    465  2HB  CYS      2       18.758  18.253  -12.959  0.00  0.00           H
ATOM    466  N    CYS      3       15.761  19.098  -11.885  0.00  0.00           N
ATOM    467  CA   CYS      3       14.518  19.828  -11.470  0.00  0.00           C
ATOM    468  C    CYS      3       13.220  18.988  -11.158  0.00  0.00           C
ATOM    469  O    CYS      3       12.535  19.264  -10.171  0.00  0.00           O
ATOM    470  CB   CYS      3       14.242  20.788  -12.652  0.00  0.00           C
ATOM    471  SG   CYS      3       15.309  22.251  -12.667  0.00  0.00           S
ATOM    472  H    CYS      3       16.193  19.251  -12.802  0.00  0.00           H
```

FIG. 8 - 15

```
ATOM    473  HA  CYS     3      14.710  20.428 -10.545  0.00  0.00           H
ATOM    474 1HB  CYS     3      14.297  20.289 -13.638  0.00  0.00           H
ATOM    475 2HB  CYS     3      13.196  21.138 -12.602  0.00  0.00           H
ATOM    476  N   SER     4      12.896  17.981 -11.985  0.00  0.00           N
ATOM    477  CA  SER     4      11.833  16.981 -11.696  0.00  0.00           C
ATOM    478  C   SER     4      12.098  15.927 -10.557  0.00  0.00           C
ATOM    479  O   SER     4      11.175  15.210 -10.172  0.00  0.00           O
ATOM    480  CB  SER     4      11.493  16.321 -13.054  0.00  0.00           C
ATOM    481  OG  SER     4      12.458  15.352 -13.475  0.00  0.00           O
ATOM    482  H   SER     4      13.623  17.767 -12.661  0.00  0.00           H
ATOM    483  HA  SER     4      10.925  17.528 -11.374  0.00  0.00           H
ATOM    484 1HB  SER     4      10.520  15.823 -12.947  0.00  0.00           H
ATOM    485 2HB  SER     4      11.325  17.075 -13.848  0.00  0.00           H
ATOM    486  HG  SER     4      12.587  14.760 -12.717  0.00  0.00           H
ATOM    487  N   ASN     5      13.298  15.890  -9.954  0.00  0.00           N
ATOM    488  CA  ASN     5      13.520  15.271  -8.631  0.00  0.00           C
ATOM    489  C   ASN     5      13.249  16.320  -7.492  0.00  0.00           C
ATOM    490  O   ASN     5      13.496  17.514  -7.700  0.00  0.00           O
ATOM    491  CB  ASN     5      15.027  14.909  -8.516  0.00  0.00           C
ATOM    492  CG  ASN     5      15.650  13.872  -9.436  0.00  0.00           C
ATOM    493 OD1 ASN     5      15.196  13.528 -10.518  0.00  0.00           O
ATOM    494 ND2 ASN     5      16.748  13.339  -8.977  0.00  0.00           N
ATOM    495  H   ASN     5      14.052  16.431 -10.390  0.00  0.00           H
ATOM    496  HA  ASN     5      12.876  14.376  -8.486  0.00  0.00           H
ATOM    497 1HB  ASN     5      15.673  15.813  -8.516  0.00  0.00           H
ATOM    498 2HB  ASN     5      15.157  14.500  -7.513  0.00  0.00           H
ATOM    499 1HD2 ASN     5      16.916  12.434  -9.409  0.00  0.00           H
ATOM    500 2HD2 ASN     5      16.959  13.603  -8.009  0.00  0.00           H
ATOM    501  N   PRO     6      12.853  15.946  -6.246  0.00  0.00           N
ATOM    502  CA  PRO     6      12.790  16.921  -5.117  0.00  0.00           C
ATOM    503  C   PRO     6      14.122  17.558  -4.592  0.00  0.00           C
ATOM    504  O   PRO     6      14.104  18.620  -3.975  0.00  0.00           O
ATOM    505  CB  PRO     6      11.974  16.138  -4.077  0.00  0.00           C
ATOM    506  CG  PRO     6      12.134  14.661  -4.400  0.00  0.00           C
```

FIG. 8 - 16

```
ATOM    507  CD  PRO     6      12.460  14.569  -5.892  0.00  0.00           C
ATOM    508  HA  PRO     6      12.198  17.787  -5.426  0.00  0.00           H
ATOM    509 1HB  PRO     6      12.237  16.397  -3.035  0.00  0.00           H
ATOM    510 2HB  PRO     6      10.906  16.346  -4.172  0.00  0.00           H
ATOM    511 1HG  PRO     6      12.949  14.294  -3.782  0.00  0.00           H
ATOM    512 2HG  PRO     6      11.258  14.055  -4.114  0.00  0.00           H
ATOM    513 1HD  PRO     6      13.254  13.829  -6.078  0.00  0.00           H
ATOM    514 2HD  PRO     6      11.608  14.236  -6.509  0.00  0.00           H
ATOM    515  N   VAL     7      15.274  16.948  -4.875  0.00  0.00           N
ATOM    516  CA  VAL     7      16.521  17.139  -4.081  0.00  0.00           C
ATOM    517  C   VAL     7      17.575  17.995  -4.822  0.00  0.00           C
ATOM    518  O   VAL     7      17.963  19.052  -4.324  0.00  0.00           O
ATOM    519  CB  VAL     7      16.989  15.709  -3.620  0.00  0.00           C
ATOM    520  CG1 VAL     7      18.420  15.642  -3.030  0.00  0.00           C
ATOM    521  CG2 VAL     7      16.065  15.088  -2.543  0.00  0.00           C
ATOM    522  H   VAL     7      15.101  16.079  -5.379  0.00  0.00           H
ATOM    523  HA  VAL     7      16.306  17.787  -3.217  0.00  0.00           H
ATOM    524  HB  VAL     7      16.958  15.048  -4.522  0.00  0.00           H
ATOM    525 1HG1 VAL     7      18.532  16.285  -2.135  0.00  0.00           H
ATOM    526 2HG1 VAL     7      18.699  14.615  -2.721  0.00  0.00           H
ATOM    527 3HG1 VAL     7      19.193  15.960  -3.755  0.00  0.00           H
ATOM    528 1HG2 VAL     7      15.013  15.025  -2.874  0.00  0.00           H
ATOM    529 2HG2 VAL     7      16.366  14.057  -2.274  0.00  0.00           H
ATOM    530 3HG2 VAL     7      16.063  15.676  -1.604  0.00  0.00           H
ATOM    531  N   CYS     8      18.035  17.582  -6.014  0.00  0.00           N
ATOM    532  CA  CYS     8      18.938  18.422  -6.846  0.00  0.00           C
ATOM    533  C   CYS     8      18.366  19.678  -7.571  0.00  0.00           C
ATOM    534  O   CYS     8      19.057  20.660  -7.856  0.00  0.00           O
ATOM    535  CB  CYS     8      19.809  17.525  -7.738  0.00  0.00           C
ATOM    536  SG  CYS     8      18.825  17.034  -9.159  0.00  0.00           S
ATOM    537  H   CYS     8      17.562  16.755  -6.347  0.00  0.00           H
ATOM    538  HA  CYS     8      19.520  18.894  -6.080  0.00  0.00           H
ATOM    539 1HB  CYS     8      20.710  18.063  -8.085  0.00  0.00           H
ATOM    540 2HB  CYS     8      20.183  16.631  -7.200  0.00  0.00           H
```

FIG. 8 - 17

```
ATOM    541  N   HIS   9      17.051  19.656  -7.725  0.00  0.00      N
ATOM    542  CA  HIS   9      16.148  20.838  -7.697  0.00  0.00      C
ATOM    543  C   HIS   9      16.469  21.904  -6.631  0.00  0.00      C
ATOM    544  O   HIS   9      16.546  23.092  -6.899  0.00  0.00      O
ATOM    545  CB  HIS   9      14.734  20.263  -7.519  0.00  0.00      C
ATOM    546  CG  HIS   9      13.407  20.846  -7.036  0.00  0.00      C
ATOM    547  ND1 HIS   9      12.224  20.266  -7.455  0.00  0.00      N
ATOM    548  CD2 HIS   9      13.209  22.204  -6.911  0.00  0.00      C
ATOM    549  CE1 HIS   9      11.446  21.377  -7.666  0.00  0.00      C
ATOM    550  NE2 HIS   9      11.929  22.588  -7.275  0.00  0.00      N
ATOM    551  H   HIS   9      16.703  18.728  -7.484  0.00  0.00      H
ATOM    552  HA  HIS   9      16.114  21.253  -8.669  0.00  0.00      H
ATOM    553  1HB HIS   9      14.624  19.560  -8.258  0.00  0.00      H
ATOM    554  2HB HIS   9      14.899  19.593  -6.691  0.00  0.00      H
ATOM    555  HD1 HIS   9      12.170  19.386  -7.993  0.00  0.00      H
ATOM    556  HD2 HIS   9      14.088  22.797  -6.943  0.00  0.00      H
ATOM    557  HE1 HIS   9      10.657  21.358  -8.411  0.00  0.00      H
ATOM    558  HE2 HIS   9      11.478  23.514  -7.257  1.00  0.00      H
ATOM    559  N   LEU  10      16.510  21.400  -5.416  0.00  0.00      N
ATOM    560  CA  LEU  10      16.570  22.253  -4.174  0.00  0.00      C
ATOM    561  C   LEU  10      17.979  22.645  -3.618  0.00  0.00      C
ATOM    562  O   LEU  10      18.136  23.712  -3.025  0.00  0.00      O
ATOM    563  CB  LEU  10      15.554  21.758  -3.114  0.00  0.00      C
ATOM    564  CG  LEU  10      14.053  21.915  -3.487  0.00  0.00      C
ATOM    565  CD1 LEU  10      13.157  21.366  -2.376  0.00  0.00      C
ATOM    566  CD2 LEU  10      13.618  23.365  -3.798  0.00  0.00      C
ATOM    567  H   LEU  10      16.467  20.363  -5.592  0.00  0.00      H
ATOM    568  HA  LEU  10      16.207  23.258  -4.449  0.00  0.00      H
ATOM    569  1HB LEU  10      15.773  20.698  -2.875  0.00  0.00      H
ATOM    570  2HB LEU  10      15.731  22.300  -2.164  0.00  0.00      H
ATOM    571  HG  LEU  10      13.860  21.281  -4.370  0.00  0.00      H
ATOM    572  1HD1 LEU  10      13.400  20.312  -2.145  0.00  0.00      H
ATOM    573  2HD1 LEU  10      13.255  21.943  -1.438  0.00  0.00      H
ATOM    574  3HD1 LEU  10      12.092  21.384  -2.670  0.00  0.00      H
```

FIG. 8 - 18

```
ATOM    575 1HD2 LEU  10      13.811  24.049  -2.951  0.00  0.00           H
ATOM    576 2HD2 LEU  10      14.133  23.792  -4.676  0.00  0.00           H
ATOM    577 3HD2 LEU  10      12.537  23.430  -4.028  0.00  0.00           H
ATOM    578  N   GLU  11      19.031  21.902  -3.966  0.00  0.00           N
ATOM    579  CA  GLU  11      20.375  22.455  -4.234  0.00  0.00           C
ATOM    580  C   GLU  11      20.491  23.666  -5.226  0.00  0.00           C
ATOM    581  O   GLU  11      21.376  24.511  -5.104  0.00  0.00           O
ATOM    582  CB  GLU  11      21.076  21.236  -4.876  0.00  0.00           C
ATOM    583  CG  GLU  11      21.574  20.070  -3.990  0.00  0.00           C
ATOM    584  CD  GLU  11      22.277  18.962  -4.782  0.00  0.00           C
ATOM    585  OE1 GLU  11      22.450  18.994  -6.002  0.00  0.00           O
ATOM    586  OE2 GLU  11      22.675  17.938  -3.979  0.00  0.00           O
ATOM    587  H   GLU  11      18.899  20.884  -4.054  1.00  0.00           H
ATOM    588  HA  GLU  11      20.867  22.751  -3.302  0.00  0.00           H
ATOM    589  1HB GLU  11      20.482  20.839  -5.720  0.00  0.00           H
ATOM    590  2HB GLU  11      21.935  21.634  -5.387  0.00  0.00           H
ATOM    591  1HG GLU  11      22.256  20.449  -3.207  0.00  0.00           H
ATOM    592  2HG GLU  11      20.713  19.633  -3.461  0.00  0.00           H
ATOM    593  HE2 GLU  11      23.106  17.244  -4.479  0.00  0.00           H
ATOM    594  N   HIS  12      19.661  23.658  -6.276  0.00  0.00           N
ATOM    595  CA  HIS  12      19.662  24.699  -7.333  0.00  0.00           C
ATOM    596  C   HIS  12      18.259  25.379  -7.429  0.00  0.00           C
ATOM    597  O   HIS  12      17.553  25.276  -8.431  0.00  0.00           O
ATOM    598  CB  HIS  12      20.149  24.048  -8.654  0.00  0.00           C
ATOM    599  CG  HIS  12      21.537  23.388  -8.644  0.00  0.00           C
ATOM    600  ND1 HIS  12      21.694  22.016  -8.527  0.00  0.00           N
ATOM    601  CD2 HIS  12      22.786  24.026  -8.503  0.00  0.00           C
ATOM    602  CE1 HIS  12      23.042  21.920  -8.284  0.00  0.00           C
ATOM    603  NE2 HIS  12      23.784  23.076  -8.286  0.00  0.00           N
ATOM    604  H   HIS  12      18.898  22.991  -6.129  0.00  0.00           H
ATOM    605  HA  HIS  12      20.366  25.499  -7.078  0.00  0.00           H
ATOM    606  1HB HIS  12      19.390  23.298  -8.934  0.00  0.00           H
ATOM    607  2HB HIS  12      20.103  24.812  -9.453  0.00  0.00           H
ATOM    608  HD1 HIS  12      20.950  21.320  -8.367  0.00  0.00           H
```

FIG. 8 - 19

```
ATOM    609  HD2 HIS  12      22.921  25.104  -8.459  0.00  0.00           H
ATOM    610  HE1 HIS  12      23.498  20.961  -8.028  0.00  0.00           H
ATOM    611  HE2 HIS  12      24.798  23.206  -8.161  1.00  0.00           H
ATOM    612  N   SER  13      17.833  26.009  -6.331  0.00  0.00           N
ATOM    613  CA  SER  13      16.403  26.311  -6.059  0.00  0.00           C
ATOM    614  C   SER  13      15.718  27.474  -6.816  0.00  0.00           C
ATOM    615  O   SER  13      14.613  27.336  -7.338  0.00  0.00           O
ATOM    616  CB  SER  13      16.189  26.389  -4.527  0.00  0.00           C
ATOM    617  OG  SER  13      16.891  27.498  -3.959  0.00  0.00           O
ATOM    618  H   SER  13      18.343  25.629  -5.549  0.00  0.00           H
ATOM    619  HA  SER  13      15.909  25.433  -6.445  0.00  0.00           H
ATOM    620  1HB SER  13      15.108  26.478  -4.299  0.00  0.00           H
ATOM    621  2HB SER  13      16.516  25.458  -4.029  0.00  0.00           H
ATOM    622  HG  SER  13      16.656  27.563  -3.024  0.00  0.00           H
ATOM    623  N   ASN  14      16.478  28.547  -6.968  0.00  0.00           N
ATOM    624  CA  ASN  14      16.319  29.509  -8.097  0.00  0.00           C
ATOM    625  C   ASN  14      16.196  28.900  -9.538  0.00  0.00           C
ATOM    626  O   ASN  14      15.449  29.428 -10.362  0.00  0.00           O
ATOM    627  CB  ASN  14      17.433  30.582  -7.913  0.00  0.00           C
ATOM    628  CG  ASN  14      17.510  31.688  -8.972  0.00  0.00           C
ATOM    629  OD1 ASN  14      16.857  32.717  -8.883  0.00  0.00           O
ATOM    630  ND2 ASN  14      18.299  31.511 -10.004  0.00  0.00           N
ATOM    631  H   ASN  14      17.359  28.256  -6.537  0.00  0.00           H
ATOM    632  HA  ASN  14      15.350  29.999  -7.960  0.00  0.00           H
ATOM    633  1HB ASN  14      17.269  31.099  -6.949  0.00  0.00           H
ATOM    634  2HB ASN  14      18.427  30.117  -7.799  0.00  0.00           H
ATOM    635  1HD2 ASN  14     18.192  32.224 -10.730  0.00  0.00           H
ATOM    636  2HD2 ASN  14     18.688  30.575 -10.121  0.00  0.00           H
ATOM    637  N   LEU  15      16.899  27.804  -9.844  0.00  0.00           N
ATOM    638  CA  LEU  15      16.899  27.204 -11.194  0.00  0.00           C
ATOM    639  C   LEU  15      15.745  26.168 -11.474  0.00  0.00           C
ATOM    640  O   LEU  15      15.452  25.855 -12.628  0.00  0.00           O
ATOM    641  CB  LEU  15      18.308  26.575 -11.310  0.00  0.00           C
ATOM    642  CG  LEU  15      19.596  27.407 -11.027  0.00  0.00           C
```

FIG. 8 - 20

```
ATOM    643  CD1 LEU    15      19.847  28.470 -12.110  0.00  0.00           C
ATOM    644  CD2 LEU    15      19.880  28.024  -9.646  0.00  0.00           C
ATOM    645  H   LEU    15      17.547  27.387  -9.148  0.00  0.00           H
ATOM    646  HA  LEU    15      16.807  27.999 -11.955  0.00  0.00           H
ATOM    647  1HB LEU    15      18.335  25.661 -10.691  0.00  0.00           H
ATOM    648  2HB LEU    15      18.393  26.174 -12.340  0.00  0.00           H
ATOM    649  HG  LEU    15      20.330  26.619 -11.036  0.00  0.00           H
ATOM    650 1HD1 LEU    15      19.819  28.049 -13.131  0.00  0.00           H
ATOM    651 2HD1 LEU    15      19.082  29.271 -12.079  0.00  0.00           H
ATOM    652 3HD1 LEU    15      20.828  28.970 -11.997  0.00  0.00           H
ATOM    653 1HD2 LEU    15      19.668  27.333  -8.816  0.00  0.00           H
ATOM    654 2HD2 LEU    15      20.941  28.329  -9.548  0.00  0.00           H
ATOM    655 3HD2 LEU    15      19.291  28.937  -9.474  0.00  0.00           H
ATOM    656  N   CYS    16      15.133  25.607 -10.417  0.00  0.00           N
ATOM    657  CA  CYS    16      13.992  24.663 -10.501  0.00  0.00           C
ATOM    658  C   CYS    16      12.652  25.054  -9.780  0.00  0.00           C
ATOM    659  O   CYS    16      11.655  24.340  -9.888  0.00  0.00           O
ATOM    660  CB  CYS    16      14.550  23.376  -9.879  0.00  0.00           C
ATOM    661  SG  CYS    16      15.932  22.694 -10.819  0.00  0.00           S
ATOM    662  H   CYS    16      15.599  25.875  -9.541  0.00  0.00           H
ATOM    663  HA  CYS    16      13.717  24.466 -11.556  0.00  0.00           H
ATOM    664 1HB CYS    16      14.829  23.538  -8.822  0.00  0.00           H
ATOM    665 2HB CYS    16      13.759  22.619  -9.861  0.00  0.00           H
TER     666      CYS    16
HETATM  667  N   NH2    17H     12.537  26.071  -8.951  0.00  0.00           N
HETATM  668 1HN NH2    17H     11.572  26.337  -8.734  0.00  0.00           H
HETATM  669 2HN NH2    17H     13.382  26.635  -8.774  0.00  0.00           H
ENDMDL
MODEL        4
ATOM    670  N   GLY     1      15.059  14.027 -13.141  0.00  0.00           N
ATOM    671  CA  GLY     1      16.088  14.977 -12.615  0.00  0.00           C
ATOM    672  C   GLY     1      16.607  16.088 -13.554  0.00  0.00           C
ATOM    673  O   GLY     1      16.438  16.002 -14.763  0.00  0.00           O
ATOM    674 1H  GLY     1      15.438  13.528 -13.958  1.00  0.00           H
```

FIG. 8 - 21

```
ATOM    675  2H  GLY   1      14.811  13.347 -12.408  1.00  0.00           H
ATOM    676  3H  GLY   1      14.217  14.552 -13.420  1.00  0.00           H
ATOM    677 1HA  GLY   1      15.688  15.490 -11.727  0.00  0.00           H
ATOM    678 2HA  GLY   1      16.985  14.427 -12.274  0.00  0.00           H
ATOM    679   N  CYS   2      17.317  17.140 -13.128  0.00  0.00           N
ATOM    680  CA  CYS   2      17.660  17.441 -11.707  0.00  0.00           C
ATOM    681   C  CYS   2      16.577  18.357 -11.003  0.00  0.00           C
ATOM    682   O  CYS   2      16.057  17.970  -9.960  0.00  0.00           O
ATOM    683  CB  CYS   2      19.087  18.023 -11.778  0.00  0.00           C
ATOM    684  SG  CYS   2      19.488  19.059 -10.356  0.00  0.00           S
ATOM    685   H  CYS   2      17.952  17.439 -13.870  0.00  0.00           H
ATOM    686  HA  CYS   2      17.739  16.520 -11.099  0.00  0.00           H
ATOM    687 1HB  CYS   2      19.835  17.233 -11.962  0.00  0.00           H
ATOM    688 2HB  CYS   2      19.192  18.713 -12.639  0.00  0.00           H
ATOM    689   N  CYS   3      16.172  19.501 -11.591  0.00  0.00           N
ATOM    690  CA  CYS   3      14.858  20.181 -11.315  0.00  0.00           C
ATOM    691   C  CYS   3      13.556  19.293 -11.198  0.00  0.00           C
ATOM    692   O  CYS   3      12.729  19.511 -10.314  0.00  0.00           O
ATOM    693  CB  CYS   3      14.701  21.143 -12.519  0.00  0.00           C
ATOM    694  SG  CYS   3      15.742  22.618 -12.416  0.00  0.00           S
ATOM    695   H  CYS   3      16.653  19.656 -12.483  0.00  0.00           H
ATOM    696  HA  CYS   3      14.900  20.786 -10.365  0.00  0.00           H
ATOM    697 1HB  CYS   3      14.874  20.648 -13.495  0.00  0.00           H
ATOM    698 2HB  CYS   3      13.652  21.479 -12.589  0.00  0.00           H
ATOM    699   N  SER   4      13.380  18.294 -12.069  0.00  0.00           N
ATOM    700  CA  SER   4      12.337  17.247 -11.953  0.00  0.00           C
ATOM    701   C  SER   4      12.583  16.081 -10.925  0.00  0.00           C
ATOM    702   O  SER   4      11.776  15.161 -10.816  0.00  0.00           O
ATOM    703  CB  SER   4      12.180  16.771 -13.416  0.00  0.00           C
ATOM    704  OG  SER   4      13.362  16.213 -14.006  0.00  0.00           O
ATOM    705   H  SER   4      14.140  18.118 -12.711  0.00  0.00           H
ATOM    706  HA  SER   4      11.376  17.710 -11.649  0.00  0.00           H
ATOM    707 1HB  SER   4      11.392  16.022 -13.435  0.00  0.00           H
ATOM    708 2HB  SER   4      11.793  17.598 -14.050  0.00  0.00           H
```

FIG. 8 - 22

```
ATOM    709  HG  SER     4      13.280  16.362 -14.961  0.00  0.00           H
ATOM    710  N   ASN     5      13.663  16.130 -10.132  0.00  0.00           N
ATOM    711  CA  ASN     5      13.771  15.482  -8.819  0.00  0.00           C
ATOM    712  C   ASN     5      13.274  16.354  -7.604  0.00  0.00           C
ATOM    713  O   ASN     5      13.227  17.582  -7.725  0.00  0.00           O
ATOM    714  CB  ASN     5      15.272  15.177  -8.665  0.00  0.00           C
ATOM    715  CG  ASN     5      15.813  13.824  -9.019  0.00  0.00           C
ATOM    716  OD1 ASN     5      15.655  13.286 -10.110  0.00  0.00           O
ATOM    717  ND2 ASN     5      16.627  13.356  -8.136  0.00  0.00           N
ATOM    718  H   ASN     5      14.351  16.885 -10.257  0.00  0.00           H
ATOM    719  HA  ASN     5      13.279  14.509  -8.837  0.00  0.00           H
ATOM    720  1HB ASN     5      15.839  15.643  -9.453  0.00  0.00           H
ATOM    721  2HB ASN     5      15.718  15.760  -7.862  0.00  0.00           H
ATOM    722  1HD2 ASN    5      17.292  12.729  -8.579  0.00  0.00           H
ATOM    723  2HD2 ASN    5      16.770  13.982  -7.339  0.00  0.00           H
ATOM    724  N   PRO     6      13.033  15.795  -6.384  0.00  0.00           N
ATOM    725  CA  PRO     6      12.918  16.608  -5.133  0.00  0.00           C
ATOM    726  C   PRO     6      14.176  17.432  -4.697  0.00  0.00           C
ATOM    727  O   PRO     6      14.142  18.652  -4.532  0.00  0.00           O
ATOM    728  CB  PRO     6      12.462  15.536  -4.132  0.00  0.00           C
ATOM    729  CG  PRO     6      13.138  14.255  -4.628  0.00  0.00           C
ATOM    730  CD  PRO     6      12.950  14.337  -6.142  0.00  0.00           C
ATOM    731  HA  PRO     6      12.111  17.331  -5.196  0.00  0.00           H
ATOM    732  1HB PRO     6      12.706  15.819  -3.096  0.00  0.00           H
ATOM    733  2HB PRO     6      11.358  15.424  -4.160  0.00  0.00           H
ATOM    734  1HG PRO     6      14.207  14.219  -4.357  0.00  0.00           H
ATOM    735  2HG PRO     6      12.724  13.350  -4.179  0.00  0.00           H
ATOM    736  1HD PRO     6      13.686  13.735  -6.697  0.00  0.00           H
ATOM    737  2HD PRO     6      11.963  13.945  -6.447  0.00  0.00           H
ATOM    738  N   VAL     7      15.287  16.727  -4.527  0.00  0.00           N
ATOM    739  CA  VAL     7      16.473  17.203  -3.754  0.00  0.00           C
ATOM    740  C   VAL     7      17.494  17.972  -4.639  0.00  0.00           C
ATOM    741  O   VAL     7      17.908  19.082  -4.298  0.00  0.00           O
ATOM    742  CB  VAL     7      17.035  15.938  -3.008  0.00  0.00           C
```

FIG. 8 - 23

```
ATOM    743  CG1 VAL     7      18.444  16.107  -2.391  0.00  0.00           C
ATOM    744  CG2 VAL     7      16.123  15.465  -1.846  0.00  0.00           C
ATOM    745  H   VAL     7      15.073  15.735  -4.666  0.00  0.00           H
ATOM    746  HA  VAL     7      16.163  17.974  -3.025  0.00  0.00           H
ATOM    747  HB  VAL     7      17.084  15.114  -3.759  0.00  0.00           H
ATOM    748 1HG1 VAL     7      18.477  16.921  -1.640  0.00  0.00           H
ATOM    749 2HG1 VAL     7      18.791  15.188  -1.879  0.00  0.00           H
ATOM    750 3HG1 VAL     7      19.215  16.339  -3.150  0.00  0.00           H
ATOM    751 1HG2 VAL     7      15.092  15.246  -2.175  0.00  0.00           H
ATOM    752 2HG2 VAL     7      16.496  14.537  -1.371  0.00  0.00           H
ATOM    753 3HG2 VAL     7      16.043  16.224  -1.042  0.00  0.00           H
ATOM    754  N   CYS     8      17.872  17.417  -5.801  0.00  0.00           N
ATOM    755  CA  CYS     8      18.690  18.144  -6.806  0.00  0.00           C
ATOM    756  C   CYS     8      18.141  19.445  -7.453  0.00  0.00           C
ATOM    757  O   CYS     8      18.886  20.369  -7.801  0.00  0.00           O
ATOM    758  CB  CYS     8      19.262  17.142  -7.829  0.00  0.00           C
ATOM    759  SG  CYS     8      20.430  17.943  -8.964  0.00  0.00           S
ATOM    760  H   CYS     8      17.471  16.494  -5.905  0.00  0.00           H
ATOM    761  HA  CYS     8      19.446  18.554  -6.162  0.00  0.00           H
ATOM    762 1HB  CYS     8      19.796  16.318  -7.316  0.00  0.00           H
ATOM    763 2HB  CYS     8      18.456  16.672  -8.422  0.00  0.00           H
ATOM    764  N   HIS     9      16.820  19.532  -7.478  0.00  0.00           N
ATOM    765  CA  HIS     9      16.058  20.785  -7.639  0.00  0.00           C
ATOM    766  C   HIS     9      16.432  21.874  -6.583  0.00  0.00           C
ATOM    767  O   HIS     9      16.545  23.049  -6.912  0.00  0.00           O
ATOM    768  CB  HIS     9      14.568  20.330  -7.633  0.00  0.00           C
ATOM    769  CG  HIS     9      13.315  21.162  -7.325  0.00  0.00           C
ATOM    770  ND1 HIS     9      12.106  20.860  -7.921  0.00  0.00           N
ATOM    771  CD2 HIS     9      13.245  22.449  -6.805  0.00  0.00           C
ATOM    772  CE1 HIS     9      11.426  22.044  -7.783  0.00  0.00           C
ATOM    773  NE2 HIS     9      12.016  23.041  -7.059  0.00  0.00           N
ATOM    774  H   HIS     9      16.398  18.684  -7.112  0.00  0.00           H
ATOM    775  HA  HIS     9      16.314  21.166  -8.612  0.00  0.00           H
ATOM    776 1HB  HIS     9      14.400  19.630  -8.462  0.00  0.00           H
```

FIG. 8 - 24

```
ATOM    777 2HB  HIS     9      14.521  19.702  -6.724  0.00  0.00           H
ATOM    778  HD1 HIS     9      11.953  20.120  -8.627  0.00  0.00           H
ATOM    779  HD2 HIS     9      14.140  22.947  -6.513  0.00  0.00           H
ATOM    780  HE1 HIS     9      10.553  22.263  -8.397  0.00  0.00           H
ATOM    781  HE2 HIS     9      11.653  23.964  -6.782  1.00  0.00           H
ATOM    782  N   LEU    10      16.546  21.463  -5.324  0.00  0.00           N
ATOM    783  CA  LEU    10      16.623  22.400  -4.150  0.00  0.00           C
ATOM    784  C   LEU    10      18.044  22.887  -3.719  0.00  0.00           C
ATOM    785  O   LEU    10      18.250  24.063  -3.425  0.00  0.00           O
ATOM    786  CB  LEU    10      15.738  21.856  -2.997  0.00  0.00           C
ATOM    787  CG  LEU    10      14.210  21.820  -3.281  0.00  0.00           C
ATOM    788  CD1 LEU    10      13.479  21.043  -2.182  0.00  0.00           C
ATOM    789  CD2 LEU    10      13.585  23.223  -3.405  0.00  0.00           C
ATOM    790  H   LEU    10      16.738  20.438  -5.338  0.00  0.00           H
ATOM    791  HA  LEU    10      16.171  23.354  -4.450  0.00  0.00           H
ATOM    792 1HB  LEU    10      16.096  20.843  -2.724  0.00  0.00           H
ATOM    793 2HB  LEU    10      15.908  22.460  -2.084  0.00  0.00           H
ATOM    794  HG  LEU    10      14.032  21.269  -4.225  0.00  0.00           H
ATOM    795 1HD1 LEU    10      13.852  20.005  -2.103  0.00  0.00           H
ATOM    796 2HD1 LEU    10      13.592  21.515  -1.188  0.00  0.00           H
ATOM    797 3HD1 LEU    10      12.394  20.969  -2.390  0.00  0.00           H
ATOM    798 1HD2 LEU    10      13.717  23.821  -2.483  0.00  0.00           H
ATOM    799 2HD2 LEU    10      14.019  23.816  -4.230  0.00  0.00           H
ATOM    800 3HD2 LEU    10      12.498  23.174  -3.604  0.00  0.00           H
ATOM    801  N   GLU    11      19.064  22.049  -3.869  0.00  0.00           N
ATOM    802  CA  GLU    11      20.407  22.421  -4.348  0.00  0.00           C
ATOM    803  C   GLU    11      20.611  23.577  -5.381  0.00  0.00           C
ATOM    804  O   GLU    11      21.633  24.262  -5.396  0.00  0.00           O
ATOM    805  CB  GLU    11      20.904  21.063  -4.913  0.00  0.00           C
ATOM    806  CG  GLU    11      22.043  20.408  -4.142  0.00  0.00           C
ATOM    807  CD  GLU    11      23.392  21.124  -4.207  0.00  0.00           C
ATOM    808  OE1 GLU    11      23.970  21.378  -5.261  0.00  0.00           O
ATOM    809  OE2 GLU    11      23.864  21.448  -2.976  0.00  0.00           O
ATOM    810  H   GLU    11      18.903  21.059  -3.632  1.00  0.00           H
```

FIG. 8 - 25

```
ATOM    811  HA  GLU  11      20.992  22.636  -3.467  0.00  0.00           H
ATOM    812 1HB  GLU  11      20.136  20.298  -4.896  0.00  0.00           H
ATOM    813 2HB  GLU  11      21.058  21.108  -5.979  0.00  0.00           H
ATOM    814 1HG  GLU  11      21.626  20.358  -3.123  0.00  0.00           H
ATOM    815 2HG  GLU  11      22.187  19.361  -4.460  0.00  0.00           H
ATOM    816  HE2 GLU  11      24.707  21.898  -3.059  0.00  0.00           H
ATOM    817  N   HIS  12      19.654  23.710  -6.305  0.00  0.00           N
ATOM    818  CA  HIS  12      19.621  24.795  -7.314  0.00  0.00           C
ATOM    819  C   HIS  12      18.222  25.501  -7.324  0.00  0.00           C
ATOM    820  O   HIS  12      17.531  25.513  -8.342  0.00  0.00           O
ATOM    821  CB  HIS  12      20.018  24.166  -8.678  0.00  0.00           C
ATOM    822  CG  HIS  12      21.374  23.448  -8.768  0.00  0.00           C
ATOM    823  ND1 HIS  12      21.457  22.077  -8.581  0.00  0.00           N
ATOM    824  CD2 HIS  12      22.641  24.039  -8.569  0.00  0.00           C
ATOM    825  CE1 HIS  12      22.760  21.953  -8.167  0.00  0.00           C
ATOM    826  NE2 HIS  12      23.566  23.062  -8.204  0.00  0.00           N
ATOM    827  H   HIS  12      18.833  23.143  -6.077  0.00  0.00           H
ATOM    828  HA  HIS  12      20.351  25.575  -7.065  0.00  0.00           H
ATOM    829 1HB  HIS  12      19.212  23.457  -8.930  0.00  0.00           H
ATOM    830 2HB  HIS  12      19.957  24.955  -9.448  0.00  0.00           H
ATOM    831  HD1 HIS  12      20.664  21.458  -8.363  0.00  0.00           H
ATOM    832  HD2 HIS  12      22.804  25.108  -8.488  0.00  0.00           H
ATOM    833  HE1 HIS  12      23.070  21.065  -7.611  0.00  0.00           H
ATOM    834  HE2 HIS  12      24.575  23.149  -8.014  1.00  0.00           H
ATOM    835  N   SER  13      17.780  26.039  -6.174  0.00  0.00           N
ATOM    836  CA  SER  13      16.350  26.389  -5.936  0.00  0.00           C
ATOM    837  C   SER  13      15.727  27.559  -6.737  0.00  0.00           C
ATOM    838  O   SER  13      14.673  27.435  -7.361  0.00  0.00           O
ATOM    839  CB  SER  13      16.065  26.504  -4.420  0.00  0.00           C
ATOM    840  OG  SER  13      14.660  26.423  -4.173  0.00  0.00           O
ATOM    841  H   SER  13      18.257  25.574  -5.415  0.00  0.00           H
ATOM    842  HA  SER  13      15.839  25.519  -6.308  0.00  0.00           H
ATOM    843 1HB  SER  13      16.566  25.711  -3.840  0.00  0.00           H
ATOM    844 2HB  SER  13      16.469  27.457  -4.021  0.00  0.00           H
```

FIG. 8-25

FIG. 8 - 26

```
ATOM    845  HG  SER  13      14.469  26.944  -3.383  0.00  0.00           H
ATOM    846  N   ASN  14      16.510  28.624  -6.799  0.00  0.00           N
ATOM    847  CA  ASN  14      16.400  29.677  -7.858  0.00  0.00           C
ATOM    848  C   ASN  14      16.297  29.171  -9.339  0.00  0.00           C
ATOM    849  O   ASN  14      15.594  29.761 -10.159  0.00  0.00           O
ATOM    850  CB  ASN  14      17.594  30.671  -7.749  0.00  0.00           C
ATOM    851  CG  ASN  14      17.847  31.339  -6.396  0.00  0.00           C
ATOM    852  OD1 ASN  14      16.947  31.797  -5.707  0.00  0.00           O
ATOM    853  ND2 ASN  14      19.081  31.412  -5.971  0.00  0.00           N
ATOM    854  H   ASN  14      17.368  28.309  -6.340  0.00  0.00           H
ATOM    855  HA  ASN  14      15.465  30.229  -7.676  0.00  0.00           H
ATOM    856 1HB  ASN  14      18.516  30.175  -8.109  0.00  0.00           H
ATOM    857 2HB  ASN  14      17.428  31.499  -8.464  0.00  0.00           H
ATOM    858 1HD2 ASN  14      19.174  31.992  -5.131  0.00  0.00           H
ATOM    859 2HD2 ASN  14      19.807  31.146  -6.641  0.00  0.00           H
ATOM    860  N   LEU  15      17.010  28.082  -9.666  0.00  0.00           N
ATOM    861  CA  LEU  15      17.026  27.483 -11.024  0.00  0.00           C
ATOM    862  C   LEU  15      15.940  26.374 -11.308  0.00  0.00           C
ATOM    863  O   LEU  15      15.836  25.890 -12.437  0.00  0.00           O
ATOM    864  CB  LEU  15      18.485  26.990 -11.264  0.00  0.00           C
ATOM    865  CG  LEU  15      19.634  28.013 -10.984  0.00  0.00           C
ATOM    866  CD1 LEU  15      20.288  27.907  -9.590  0.00  0.00           C
ATOM    867  CD2 LEU  15      20.730  27.927 -12.045  0.00  0.00           C
ATOM    868  H   LEU  15      17.481  27.598  -8.889  0.00  0.00           H
ATOM    869  HA  LEU  15      16.835  28.284 -11.757  0.00  0.00           H
ATOM    870 1HB  LEU  15      18.654  26.053 -10.715  0.00  0.00           H
ATOM    871 2HB  LEU  15      18.524  26.675 -12.327  0.00  0.00           H
ATOM    872  HG  LEU  15      19.177  29.022 -11.030  0.00  0.00           H
ATOM    873 1HD1 LEU  15      19.549  27.930  -8.770  0.00  0.00           H
ATOM    874 2HD1 LEU  15      20.900  26.999  -9.470  0.00  0.00           H
ATOM    875 3HD1 LEU  15      20.961  28.769  -9.407  0.00  0.00           H
ATOM    876 1HD2 LEU  15      20.316  28.106 -13.055  0.00  0.00           H
ATOM    877 2HD2 LEU  15      21.512  28.692 -11.883  0.00  0.00           H
ATOM    878 3HD2 LEU  15      21.219  26.935 -12.055  0.00  0.00           H
```

FIG. 8 - 27

```
ATOM    879  N   CYS  16      15.159  25.949 -10.297  0.00  0.00           N
ATOM    880  CA  CYS  16      14.105  24.914 -10.420  0.00  0.00           C
ATOM    881  C   CYS  16      12.694  25.245  -9.812  0.00  0.00           C
ATOM    882  O   CYS  16      11.714  24.559 -10.098  0.00  0.00           O
ATOM    883  CB  CYS  16      14.692  23.688  -9.705  0.00  0.00           C
ATOM    884  SG  CYS  16      16.173  23.049 -10.512  0.00  0.00           S
ATOM    885  H   CYS  16      15.494  26.285  -9.387  0.00  0.00           H
ATOM    886  HA  CYS  16      13.918  24.662 -11.483  0.00  0.00           H
ATOM    887 1HB  CYS  16      14.895  23.907  -8.643  0.00  0.00           H
ATOM    888 2HB  CYS  16      13.942  22.890  -9.705  0.00  0.00           H
TER     889      CYS  16
HETATM  890  N   NH2  17H     12.497  26.173  -8.893  0.00  0.00           N
HETATM  891 1HN  NH2  17H     11.516  26.453  -8.801  0.00  0.00           H
HETATM  892 2HN  NH2  17H     13.319  26.738  -8.629  0.00  0.00           H
ENDMDL
MODEL        5
ATOM    893  N   GLY   1      15.082  13.884 -12.916  0.00  0.00           N
ATOM    894  CA  GLY   1      16.136  14.869 -12.526  0.00  0.00           C
ATOM    895  C   GLY   1      16.474  16.001 -13.521  0.00  0.00           C
ATOM    896  O   GLY   1      16.209  15.876 -14.710  0.00  0.00           O
ATOM    897  1H  GLY   1      15.364  13.403 -13.782  1.00  0.00           H
ATOM    898  2H  GLY   1      14.963  13.191 -12.162  1.00  0.00           H
ATOM    899  3H  GLY   1      14.191  14.377 -13.072  1.00  0.00           H
ATOM    900 1HA  GLY   1      15.848  15.354 -11.578  0.00  0.00           H
ATOM    901 2HA  GLY   1      17.093  14.354 -12.320  0.00  0.00           H
ATOM    902  N   CYS   2      17.112  17.122 -13.166  0.00  0.00           N
ATOM    903  CA  CYS   2      17.567  17.453 -11.785  0.00  0.00           C
ATOM    904  C   CYS   2      16.449  18.211 -10.967  0.00  0.00           C
ATOM    905  O   CYS   2      16.043  17.702  -9.923  0.00  0.00           O
ATOM    906  CB  CYS   2      18.896  18.213 -11.980  0.00  0.00           C
ATOM    907  SG  CYS   2      19.281  19.275 -10.573  0.00  0.00           S
ATOM    908  H   CYS   2      17.652  17.467 -13.961  0.00  0.00           H
ATOM    909  HA  CYS   2      17.826  16.545 -11.208  0.00  0.00           H
ATOM    910 1HB  CYS   2      19.716  17.521 -12.237  0.00  0.00           H
```

FIG. 8 - 28

```
ATOM    911  2HB CYS     2      18.840  18.911 -12.839  0.00  0.00           H
ATOM    912  N   CYS     3      15.885  19.332 -11.469  0.00  0.00           N
ATOM    913  CA  CYS     3      14.546  19.879 -11.054  0.00  0.00           C
ATOM    914  C   CYS     3      13.364  18.871 -10.769  0.00  0.00           C
ATOM    915  O   CYS     3      12.642  19.013  -9.780  0.00  0.00           O
ATOM    916  CB  CYS     3      14.152  20.800 -12.237  0.00  0.00           C
ATOM    917  SG  CYS     3      15.130  22.318 -12.370  0.00  0.00           S
ATOM    918  H   CYS     3      16.273  19.567 -12.388  0.00  0.00           H
ATOM    919  HA  CYS     3      14.634  20.513 -10.136  0.00  0.00           H
ATOM    920  1HB CYS     3      14.186  20.273 -13.212  0.00  0.00           H
ATOM    921  2HB CYS     3      13.093  21.095 -12.140  0.00  0.00           H
ATOM    922  N   SER     4      13.180  17.871 -11.643  0.00  0.00           N
ATOM    923  CA  SER     4      12.209  16.760 -11.468  0.00  0.00           C
ATOM    924  C   SER     4      12.602  15.587 -10.501  0.00  0.00           C
ATOM    925  O   SER     4      11.791  14.692 -10.261  0.00  0.00           O
ATOM    926  CB  SER     4      11.886  16.286 -12.906  0.00  0.00           C
ATOM    927  OG  SER     4      13.012  15.768 -13.627  0.00  0.00           O
ATOM    928  H   SER     4      13.887  17.821 -12.370  0.00  0.00           H
ATOM    929  HA  SER     4      11.267  17.167 -11.049  0.00  0.00           H
ATOM    930  1HB SER     4      11.103  15.516 -12.855  0.00  0.00           H
ATOM    931  2HB SER     4      11.421  17.115 -13.481  0.00  0.00           H
ATOM    932  HG  SER     4      12.782  15.844 -14.567  0.00  0.00           H
ATOM    933  N   ASN     5      13.792  15.610  -9.877  0.00  0.00           N
ATOM    934  CA  ASN     5      13.986  15.032  -8.530  0.00  0.00           C
ATOM    935  C   ASN     5      13.677  16.139  -7.456  0.00  0.00           C
ATOM    936  O   ASN     5      14.216  17.242  -7.607  0.00  0.00           O
ATOM    937  CB  ASN     5      15.486  14.688  -8.382  0.00  0.00           C
ATOM    938  CG  ASN     5      16.072  13.527  -9.162  0.00  0.00           C
ATOM    939  OD1 ASN     5      15.560  13.003 -10.144  0.00  0.00           O
ATOM    940  ND2 ASN     5      17.223  13.130  -8.710  0.00  0.00           N
ATOM    941  H   ASN     5      14.376  16.423 -10.107  0.00  0.00           H
ATOM    942  HA  ASN     5      13.363  14.128  -8.371  0.00  0.00           H
ATOM    943  1HB ASN     5      16.122  15.583  -8.534  0.00  0.00           H
ATOM    944  2HB ASN     5      15.637  14.439  -7.329  0.00  0.00           H
```

FIG. 8 - 29

```
ATOM    945 1HD2 ASN     5      17.397  12.149  -8.926  0.00  0.00           H
ATOM    946 2HD2 ASN     5      17.466  13.612  -7.838  0.00  0.00           H
ATOM    947  N   PRO     6      12.941  15.919  -6.333  0.00  0.00           N
ATOM    948  CA  PRO     6      12.804  16.952  -5.258  0.00  0.00           C
ATOM    949  C   PRO     6      14.084  17.597  -4.627  0.00  0.00           C
ATOM    950  O   PRO     6      14.104  18.780  -4.289  0.00  0.00           O
ATOM    951  CB  PRO     6      11.845  16.282  -4.265  0.00  0.00           C
ATOM    952  CG  PRO     6      11.813  14.800  -4.593  0.00  0.00           C
ATOM    953  CD  PRO     6      12.291  14.635  -6.013  0.00  0.00           C
ATOM    954  HA  PRO     6      12.288  17.810  -5.680  0.00  0.00           H
ATOM    955 1HB  PRO     6      12.099  16.499  -3.213  0.00  0.00           H
ATOM    956 2HB  PRO     6      10.819  16.634  -4.398  0.00  0.00           H
ATOM    957 1HG  PRO     6      12.502  14.277  -3.972  0.00  0.00           H
ATOM    958 2HG  PRO     6      10.832  14.329  -4.400  0.00  0.00           H
ATOM    959 1HD  PRO     6      12.945  13.756  -6.146  0.00  0.00           H
ATOM    960 2HD  PRO     6      11.407  14.435  -6.603  0.00  0.00           H
ATOM    961  N   VAL     7      15.163  16.828  -4.561  0.00  0.00           N
ATOM    962  CA  VAL     7      16.453  17.200  -3.940  0.00  0.00           C
ATOM    963  C   VAL     7      17.330  18.055  -4.875  0.00  0.00           C
ATOM    964  O   VAL     7      17.677  19.181  -4.527  0.00  0.00           O
ATOM    965  CB  VAL     7      17.105  15.830  -3.529  0.00  0.00           C
ATOM    966  CG1 VAL     7      18.549  15.947  -3.014  0.00  0.00           C
ATOM    967  CG2 VAL     7      16.328  15.047  -2.452  0.00  0.00           C
ATOM    968  H   VAL     7      15.060  15.928  -5.016  0.00  0.00           H
ATOM    969  HA  VAL     7      16.276  17.884  -3.093  0.00  0.00           H
ATOM    970  HB  VAL     7      17.128  15.187  -4.439  0.00  0.00           H
ATOM    971 1HG1 VAL     7      19.221  16.381  -3.775  0.00  0.00           H
ATOM    972 2HG1 VAL     7      18.602  16.587  -2.113  0.00  0.00           H
ATOM    973 3HG1 VAL     7      18.968  14.958  -2.752  0.00  0.00           H
ATOM    974 1HG2 VAL     7      15.296  14.824  -2.777  0.00  0.00           H
ATOM    975 2HG2 VAL     7      16.804  14.074  -2.233  0.00  0.00           H
ATOM    976 3HG2 VAL     7      16.261  15.618  -1.508  0.00  0.00           H
ATOM    977  N   CYS     8      17.692  17.538  -6.058  0.00  0.00           N
ATOM    978  CA  CYS     8      18.505  18.311  -7.037  0.00  0.00           C
```

FIG. 8 - 30

```
ATOM    979  C   CYS     8      17.930  19.620  -7.651  0.00  0.00           C
ATOM    980  O   CYS     8      18.644  20.560  -8.009  0.00  0.00           O
ATOM    981  CB  CYS     8      19.132  17.343  -8.059  0.00  0.00           C
ATOM    982  SG  CYS     8      20.270  18.203  -9.180  0.00  0.00           S
ATOM    983  H   CYS     8      17.500  16.540  -6.066  0.00  0.00           H
ATOM    984  HA  CYS     8      19.241  18.738  -6.376  0.00  0.00           H
ATOM    985  1HB CYS     8      19.705  16.550  -7.542  0.00  0.00           H
ATOM    986  2HB CYS     8      18.354  16.836  -8.658  0.00  0.00           H
ATOM    987  N   HIS     9      16.613  19.709  -7.594  0.00  0.00           N
ATOM    988  CA  HIS     9      15.829  20.966  -7.622  0.00  0.00           C
ATOM    989  C   HIS     9      16.313  22.029  -6.596  0.00  0.00           C
ATOM    990  O   HIS     9      16.459  23.204  -6.893  0.00  0.00           O
ATOM    991  CB  HIS     9      14.357  20.533  -7.434  0.00  0.00           C
ATOM    992  CG  HIS     9      13.062  21.206  -7.022  0.00  0.00           C
ATOM    993  ND1 HIS     9      11.875  20.890  -7.656  0.00  0.00           N
ATOM    994  CD2 HIS     9      13.008  22.497  -6.579  0.00  0.00           C
ATOM    995  CE1 HIS     9      11.207  22.088  -7.580  0.00  0.00           C
ATOM    996  NE2 HIS     9      11.803  23.110  -6.894  0.00  0.00           N
ATOM    997  H   HIS     9      16.214  18.808  -7.327  0.00  0.00           H
ATOM    998  HA  HIS     9      15.878  21.364  -8.592  0.00  0.00           H
ATOM    999  1HB HIS     9      14.231  19.530  -7.657  0.00  0.00           H
ATOM   1000  2HB HIS     9      14.526  20.220  -6.414  0.00  0.00           H
ATOM   1001  HD1 HIS     9      11.746  20.133  -8.348  0.00  0.00           H
ATOM   1002  HD2 HIS     9      13.974  22.917  -6.473  0.00  0.00           H
ATOM   1003  HE1 HIS     9      10.344  22.294  -8.214  0.00  0.00           H
ATOM   1004  HE2 HIS     9      11.459  24.056  -6.675  1.00  0.00           H
ATOM   1005  N   LEU    10      16.420  21.548  -5.369  0.00  0.00           N
ATOM   1006  CA  LEU    10      16.582  22.410  -4.148  0.00  0.00           C
ATOM   1007  C   LEU    10      18.038  22.815  -3.751  0.00  0.00           C
ATOM   1008  O   LEU    10      18.301  23.969  -3.412  0.00  0.00           O
ATOM   1009  CB  LEU    10      15.718  21.858  -2.983  0.00  0.00           C
ATOM   1010  CG  LEU    10      14.178  21.911  -3.196  0.00  0.00           C
ATOM   1011  CD1 LEU    10      13.455  21.184  -2.059  0.00  0.00           C
ATOM   1012  CD2 LEU    10      13.623  23.345  -3.307  0.00  0.00           C
```

FIG. 8 - 31

```
ATOM   1013  H   LEU  10      16.417  20.498  -5.496  0.00  0.00           H
ATOM   1014  HA  LEU  10      16.166  23.398  -4.383  0.00  0.00           H
ATOM   1015  1HB LEU  10      16.031  20.818  -2.770  0.00  0.00           H
ATOM   1016  2HB LEU  10      15.958  22.412  -2.054  0.00  0.00           H
ATOM   1017  HG  LEU  10      13.932  21.363  -4.124  0.00  0.00           H
ATOM   1018  1HD1 LEU  10     13.784  20.131  -1.979  0.00  0.00           H
ATOM   1019  2HD1 LEU  10     13.631  21.663  -1.078  0.00  0.00           H
ATOM   1020  3HD1 LEU  10     12.362  21.159  -2.224  0.00  0.00           H
ATOM   1021  1HD2 LEU  10     13.845  23.949  -2.407  0.00  0.00           H
ATOM   1022  2HD2 LEU  10     14.035  23.899  -4.169  0.00  0.00           H
ATOM   1023  3HD2 LEU  10     12.524  23.352  -3.440  0.00  0.00           H
ATOM   1024  N   GLU  11      19.012  21.934  -3.962  0.00  0.00           N
ATOM   1025  CA  GLU  11      20.391  22.280  -4.358  0.00  0.00           C
ATOM   1026  C   GLU  11      20.649  23.471  -5.340  0.00  0.00           C
ATOM   1027  O   GLU  11      21.649  24.182  -5.234  0.00  0.00           O
ATOM   1028  CB  GLU  11      20.836  20.951  -5.020  0.00  0.00           C
ATOM   1029  CG  GLU  11      21.004  19.711  -4.119  0.00  0.00           C
ATOM   1030  CD  GLU  11      21.969  18.646  -4.628  0.00  0.00           C
ATOM   1031  OE1 GLU  11      21.794  18.014  -5.665  0.00  0.00           O
ATOM   1032  OE2 GLU  11      23.035  18.477  -3.804  0.00  0.00           O
ATOM   1033  H   GLU  11      18.786  20.936  -3.841  1.00  0.00           H
ATOM   1034  HA  GLU  11      20.986  22.488  -3.459  0.00  0.00           H
ATOM   1035  1HB GLU  11      20.180  20.682  -5.861  0.00  0.00           H
ATOM   1036  2HB GLU  11      21.768  21.165  -5.512  0.00  0.00           H
ATOM   1037  1HG GLU  11      21.249  20.053  -3.109  0.00  0.00           H
ATOM   1038  2HG GLU  11      20.033  19.222  -3.992  0.00  0.00           H
ATOM   1039  HE2 GLU  11      23.611  17.799  -4.162  0.00  0.00           H
ATOM   1040  N   HIS  12      19.767  23.635  -6.331  0.00  0.00           N
ATOM   1041  CA  HIS  12      19.742  24.844  -7.192  0.00  0.00           C
ATOM   1042  C   HIS  12      18.316  25.480  -7.231  0.00  0.00           C
ATOM   1043  O   HIS  12      17.642  25.479  -8.261  0.00  0.00           O
ATOM   1044  CB  HIS  12      20.337  24.461  -8.565  0.00  0.00           C
ATOM   1045  CG  HIS  12      21.854  24.244  -8.603  0.00  0.00           C
ATOM   1046  ND1 HIS  12      22.445  23.004  -8.427  0.00  0.00           N
```

FIG. 8 - 32

```
ATOM   1047  CD2 HIS  12      22.845  25.248  -8.632  0.00  0.00      C
ATOM   1048  CE1 HIS  12      23.767  23.359  -8.306  0.00  0.00      C
ATOM   1049  NE2 HIS  12      24.104  24.680  -8.455  0.00  0.00      N
ATOM   1050  H   HIS  12      18.959  23.015  -6.188  0.00  0.00      H
ATOM   1051  HA  HIS  12      20.385  25.630  -6.778  0.00  0.00      H
ATOM   1052  1HB HIS  12      19.796  23.564  -8.919  0.00  0.00      H
ATOM   1053  2HB HIS  12      20.086  25.263  -9.276  0.00  0.00      H
ATOM   1054  HD1 HIS  12      21.987  22.116  -8.195  0.00  0.00      H
ATOM   1055  HD2 HIS  12      22.637  26.312  -8.698  0.00  0.00      H
ATOM   1056  HE1 HIS  12      24.520  22.618  -8.029  0.00  0.00      H
ATOM   1057  HE2 HIS  12      25.031  25.128  -8.440  1.00  0.00      H
ATOM   1058  N   SER  13      17.856  25.996  -6.080  0.00  0.00      N
ATOM   1059  CA  SER  13      16.426  26.340  -5.842  0.00  0.00      C
ATOM   1060  C   SER  13      15.797  27.491  -6.673  0.00  0.00      C
ATOM   1061  O   SER  13      14.748  27.348  -7.299  0.00  0.00      O
ATOM   1062  CB  SER  13      16.170  26.508  -4.325  0.00  0.00      C
ATOM   1063  OG  SER  13      14.769  26.465  -4.051  0.00  0.00      O
ATOM   1064  H   SER  13      18.324  25.522  -5.322  0.00  0.00      H
ATOM   1065  HA  SER  13      15.916  25.446  -6.164  0.00  0.00      H
ATOM   1066  1HB SER  13      16.665  25.719  -3.731  0.00  0.00      H
ATOM   1067  2HB SER  13      16.600  27.462  -3.961  0.00  0.00      H
ATOM   1068  HG  SER  13      14.622  26.889  -3.195  0.00  0.00      H
ATOM   1069  N   ASN  14      16.571  28.563  -6.751  0.00  0.00      N
ATOM   1070  CA  ASN  14      16.469  29.589  -7.836  0.00  0.00      C
ATOM   1071  C   ASN  14      16.367  29.063  -9.312  0.00  0.00      C
ATOM   1072  O   ASN  14      15.690  29.684 -10.132  0.00  0.00      O
ATOM   1073  CB  ASN  14      17.670  30.553  -7.611  0.00  0.00      C
ATOM   1074  CG  ASN  14      17.676  31.827  -8.458  0.00  0.00      C
ATOM   1075  OD1 ASN  14      17.103  32.843  -8.095  0.00  0.00      O
ATOM   1076  ND2 ASN  14      18.319  31.822  -9.599  0.00  0.00      N
ATOM   1077  H   ASN  14      17.433  28.239  -6.305  0.00  0.00      H
ATOM   1078  HA  ASN  14      15.535  30.150  -7.666  0.00  0.00      H
ATOM   1079  1HB ASN  14      17.677  30.902  -6.560  0.00  0.00      H
ATOM   1080  2HB ASN  14      18.633  30.021  -7.735  0.00  0.00      H
```

FIG. 8 - 33

```
ATOM   1081 1HD2 ASN  14     18.158  32.675 -10.143  0.00  0.00           H
ATOM   1082 2HD2 ASN  14     18.587  30.907  -9.960  0.00  0.00           H
ATOM   1083  N   LEU  15     17.027  27.943  -9.649  0.00  0.00           N
ATOM   1084  CA  LEU  15     16.908  27.324 -11.003  0.00  0.00           C
ATOM   1085  C   LEU  15     15.749  26.276 -11.218  0.00  0.00           C
ATOM   1086  O   LEU  15     15.544  25.822 -12.347  0.00  0.00           O
ATOM   1087  CB  LEU  15     18.298  26.763 -11.422  0.00  0.00           C
ATOM   1088  CG  LEU  15     19.535  27.704 -11.332  0.00  0.00           C
ATOM   1089  CD1 LEU  15     20.795  26.962 -11.794  0.00  0.00           C
ATOM   1090  CD2 LEU  15     19.379  28.993 -12.158  0.00  0.00           C
ATOM   1091  H   LEU  15     17.367  27.407  -8.836  0.00  0.00           H
ATOM   1092  HA  LEU  15     16.678  28.125 -11.719  0.00  0.00           H
ATOM   1093 1HB  LEU  15     18.487  25.848 -10.833  0.00  0.00           H
ATOM   1094 2HB  LEU  15     18.210  26.404 -12.467  0.00  0.00           H
ATOM   1095  HG  LEU  15     19.683  27.998 -10.274  0.00  0.00           H
ATOM   1096 1HD1 LEU  15     20.963  26.030 -11.231  0.00  0.00           H
ATOM   1097 2HD1 LEU  15     20.732  26.688 -12.865  0.00  0.00           H
ATOM   1098 3HD1 LEU  15     21.698  27.589 -11.672  0.00  0.00           H
ATOM   1099 1HD2 LEU  15     19.217  28.790 -13.234  0.00  0.00           H
ATOM   1100 2HD2 LEU  15     18.518  29.601 -11.820  0.00  0.00           H
ATOM   1101 3HD2 LEU  15     20.265  29.650 -12.083  0.00  0.00           H
ATOM   1102  N   CYS  16     15.005  25.869 -10.171  0.00  0.00           N
ATOM   1103  CA  CYS  16     13.876  24.908 -10.270  0.00  0.00           C
ATOM   1104  C   CYS  16     12.524  25.301  -9.571  0.00  0.00           C
ATOM   1105  O   CYS  16     11.492  24.684  -9.821  0.00  0.00           O
ATOM   1106  CB  CYS  16     14.421  23.618  -9.640  0.00  0.00           C
ATOM   1107  SG  CYS  16     15.790  22.911 -10.579  0.00  0.00           S
ATOM   1108  H   CYS  16     15.385  26.161  -9.268  0.00  0.00           H
ATOM   1109  HA  CYS  16     13.612  24.709 -11.329  0.00  0.00           H
ATOM   1110 1HB  CYS  16     14.721  23.789  -8.592  0.00  0.00           H
ATOM   1111 2HB  CYS  16     13.622  22.870  -9.604  0.00  0.00           H
TER    1112      CYS  16
HETATM 1113  N   NH2  17H    12.434  26.204  -8.613  0.00  0.00           N
HETATM 1114 1HN  NH2  17H    11.480  26.549  -8.471  0.00  0.00           H
```

FIG. 8 - 34

```
HETATM 1115 2HN  NH2  17H    13.304   26.706   -8.373   0.00   0.00          H
ENDMDL
MODEL        6
ATOM   1116  N   GLY    1    14.719   14.941  -15.415   0.00   0.00          N
ATOM   1117  CA  GLY    1    15.699   16.059  -15.219   0.00   0.00          C
ATOM   1118  C   GLY    1    16.046   16.375  -13.735   0.00   0.00          C
ATOM   1119  O   GLY    1    15.733   15.583  -12.847   0.00   0.00          O
ATOM   1120  1H  GLY    1    15.101   14.075  -15.010   1.00   0.00          H
ATOM   1121  2H  GLY    1    13.832   15.176  -14.948   1.00   0.00          H
ATOM   1122  3H  GLY    1    14.551   14.804  -16.422   1.00   0.00          H
ATOM   1123  1HA GLY    1    16.644   15.832  -15.752   0.00   0.00          H
ATOM   1124  2HA GLY    1    15.308   16.981  -15.693   0.00   0.00          H
ATOM   1125  N   CYS    2    16.680   17.524  -13.443   0.00   0.00          N
ATOM   1126  CA  CYS    2    17.113   17.846  -12.049   0.00   0.00          C
ATOM   1127  C   CYS    2    16.008   18.625  -11.227   0.00   0.00          C
ATOM   1128  O   CYS    2    15.642   18.187  -10.136   0.00   0.00          O
ATOM   1129  CB  CYS    2    18.465   18.570  -12.235   0.00   0.00          C
ATOM   1130  SG  CYS    2    18.896   19.621  -10.838   0.00   0.00          S
ATOM   1131  H   CYS    2    17.228   17.934  -14.208   0.00   0.00          H
ATOM   1132  HA  CYS    2    17.328   16.923  -11.474   0.00   0.00          H
ATOM   1133  1HB CYS    2    19.269   17.860  -12.493   0.00   0.00          H
ATOM   1134  2HB CYS    2    18.418   19.280  -13.084   0.00   0.00          H
ATOM   1135  N   CYS    3    15.425   19.719  -11.766   0.00   0.00          N
ATOM   1136  CA  CYS    3    14.112   20.302  -11.320   0.00   0.00          C
ATOM   1137  C   CYS    3    12.890   19.323  -11.127   0.00   0.00          C
ATOM   1138  O   CYS    3    12.071   19.555  -10.237   0.00   0.00          O
ATOM   1139  CB  CYS    3    13.805   21.352  -12.415   0.00   0.00          C
ATOM   1140  SG  CYS    3    12.295   22.321  -12.128   0.00   0.00          S
ATOM   1141  H   CYS    3    15.808   19.952  -12.687   0.00   0.00          H
ATOM   1142  HA  CYS    3    14.244   20.856  -10.351   0.00   0.00          H
ATOM   1143  1HB CYS    3    14.636   22.079  -12.513   0.00   0.00          H
ATOM   1144  2HB CYS    3    13.701   20.882  -13.412   0.00   0.00          H
ATOM   1145  N   SER    4    12.768   18.236  -11.914   0.00   0.00          N
ATOM   1146  CA  SER    4    11.796   17.143  -11.668   0.00   0.00          C
```

FIG. 8 - 35

```
ATOM   1147  C   SER   4      12.018  16.211 -10.426  0.00  0.00           C
ATOM   1148  O   SER   4      11.072  15.575  -9.963  0.00  0.00           O
ATOM   1149  CB  SER   4      11.798  16.349 -12.992  0.00  0.00           C
ATOM   1150  OG  SER   4      12.972  15.552 -13.182  0.00  0.00           O
ATOM   1151  H   SER   4      13.538  18.017 -12.543  0.00  0.00           H
ATOM   1152  HA  SER   4      10.793  17.588 -11.535  0.00  0.00           H
ATOM   1153  1HB SER   4      10.928  15.693 -12.973  0.00  0.00           H
ATOM   1154  2HB SER   4      11.618  17.006 -13.868  0.00  0.00           H
ATOM   1155  HG  SER   4      13.114  15.057 -12.358  0.00  0.00           H
ATOM   1156  N   ASN   5      13.239  16.143  -9.876  0.00  0.00           N
ATOM   1157  CA  ASN   5      13.530  15.427  -8.616  0.00  0.00           C
ATOM   1158  C   ASN   5      13.322  16.362  -7.371  0.00  0.00           C
ATOM   1159  O   ASN   5      13.540  17.572  -7.492  0.00  0.00           O
ATOM   1160  CB  ASN   5      15.038  15.047  -8.653  0.00  0.00           C
ATOM   1161  CG  ASN   5      15.526  14.030  -9.674  0.00  0.00           C
ATOM   1162  OD1 ASN   5      14.906  13.695 -10.676  0.00  0.00           O
ATOM   1163  ND2 ASN   5      16.674  13.481  -9.392  0.00  0.00           N
ATOM   1164  H   ASN   5      13.962  16.717 -10.318  0.00  0.00           H
ATOM   1165  HA  ASN   5      12.892  14.522  -8.510  0.00  0.00           H
ATOM   1166  1HB ASN   5      15.692  15.944  -8.681  0.00  0.00           H
ATOM   1167  2HB ASN   5      15.264  14.591  -7.688  0.00  0.00           H
ATOM   1168  1HD2 ASN   5      16.762  12.586  -9.864  0.00  0.00           H
ATOM   1169  2HD2 ASN   5      17.036  13.716  -8.462  0.00  0.00           H
ATOM   1170  N   PRO   6      13.015  15.870  -6.141  0.00  0.00           N
ATOM   1171  CA  PRO   6      13.007  16.740  -4.926  0.00  0.00           C
ATOM   1172  C   PRO   6      14.354  17.360  -4.424  0.00  0.00           C
ATOM   1173  O   PRO   6      14.358  18.349  -3.696  0.00  0.00           O
ATOM   1174  CB  PRO   6      12.261  15.855  -3.915  0.00  0.00           C
ATOM   1175  CG  PRO   6      12.418  14.416  -4.376  0.00  0.00           C
ATOM   1176  CD  PRO   6      12.658  14.461  -5.886  0.00  0.00           C
ATOM   1177  HA  PRO   6      12.390  17.619  -5.127  0.00  0.00           H
ATOM   1178  1HB PRO   6      12.583  16.027  -2.872  0.00  0.00           H
ATOM   1179  2HB PRO   6      11.188  16.056  -3.929  0.00  0.00           H
ATOM   1180  1HG PRO   6      13.268  14.005  -3.836  0.00  0.00           H
```

FIG. 8 - 36

```
ATOM   1181  2HG  PRO     6      11.564  13.776  -4.095  0.00  0.00           H
ATOM   1182  1HD  PRO     6      13.446  13.752  -6.185  0.00  0.00           H
ATOM   1183  2HD  PRO     6      11.772  14.172  -6.478  0.00  0.00           H
ATOM   1184  N    VAL     7      15.492  16.818  -4.851  0.00  0.00           N
ATOM   1185  CA   VAL     7      16.818  17.054  -4.230  0.00  0.00           C
ATOM   1186  C    VAL     7      17.675  17.990  -5.105  0.00  0.00           C
ATOM   1187  O    VAL     7      18.032  19.091  -4.682  0.00  0.00           O
ATOM   1188  CB   VAL     7      17.431  15.623  -4.010  0.00  0.00           C
ATOM   1189  CG1  VAL     7      18.895  15.634  -3.536  0.00  0.00           C
ATOM   1190  CG2  VAL     7      16.658  14.747  -3.007  0.00  0.00           C
ATOM   1191  H    VAL     7      15.332  15.947  -5.349  0.00  0.00           H
ATOM   1192  HA   VAL     7      16.717  17.631  -3.294  0.00  0.00           H
ATOM   1193  HB   VAL     7      17.397  15.090  -4.988  0.00  0.00           H
ATOM   1194 1HG1  VAL     7      19.557  16.139  -4.262  0.00  0.00           H
ATOM   1195 2HG1  VAL     7      18.997  16.154  -2.566  0.00  0.00           H
ATOM   1196 3HG1  VAL     7      19.288  14.608  -3.415  0.00  0.00           H
ATOM   1197 1HG2  VAL     7      15.610  14.597  -3.323  0.00  0.00           H
ATOM   1198 2HG2  VAL     7      17.106  13.740  -2.917  0.00  0.00           H
ATOM   1199 3HG2  VAL     7      16.638  15.205  -2.002  0.00  0.00           H
ATOM   1200  N    CYS     8      17.999  17.574  -6.338  0.00  0.00           N
ATOM   1201  CA   CYS     8      18.726  18.441  -7.296  0.00  0.00           C
ATOM   1202  C    CYS     8      18.083  19.776  -7.751  0.00  0.00           C
ATOM   1203  O    CYS     8      18.756  20.785  -7.989  0.00  0.00           O
ATOM   1204  CB   CYS     8      19.282  17.585  -8.452  0.00  0.00           C
ATOM   1205  SG   CYS     8      20.175  18.602  -9.658  0.00  0.00           S
ATOM   1206  H    CYS     8      17.686  16.619  -6.492  0.00  0.00           H
ATOM   1207  HA   CYS     8      19.498  18.819  -6.651  0.00  0.00           H
ATOM   1208 1HB  CYS     8      19.970  16.807  -8.068  0.00  0.00           H
ATOM   1209 2HB  CYS     8      18.469  17.053  -8.981  0.00  0.00           H
ATOM   1210  N    HIS     9      16.763  19.766  -7.728  0.00  0.00           N
ATOM   1211  CA   HIS     9      15.902  20.956  -7.678  0.00  0.00           C
ATOM   1212  C    HIS     9      16.252  21.937  -6.517  0.00  0.00           C
ATOM   1213  O    HIS     9      16.286  23.142  -6.729  0.00  0.00           O
ATOM   1214  CB   HIS     9      14.464  20.367  -7.620  0.00  0.00           C
```

FIG. 8 - 37

```
ATOM   1215  CG  HIS   9      13.181  21.026  -7.124  0.00  0.00      C
ATOM   1216  ND1 HIS   9      11.969  20.593  -7.613  0.00  0.00      N
ATOM   1217  CD2 HIS   9      13.037  22.317  -6.631  0.00  0.00      C
ATOM   1218  CE1 HIS   9      11.225  21.734  -7.506  0.00  0.00      C
ATOM   1219  NE2 HIS   9      11.743  22.785  -6.805  0.00  0.00      N
ATOM   1220  H   HIS   9      16.424  18.832  -7.509  0.00  0.00      H
ATOM   1221  HA  HIS   9      16.040  21.472  -8.610  0.00  0.00      H
ATOM   1222 1HB  HIS   9      14.287  19.728  -8.496  0.00  0.00      H
ATOM   1223 2HB  HIS   9      14.539  19.668  -6.766  0.00  0.00      H
ATOM   1224  HD1 HIS   9      11.849  19.859  -8.331  0.00  0.00      H
ATOM   1225  HD2 HIS   9      13.902  22.910  -6.443  0.00  0.00      H
ATOM   1226  HE1 HIS   9      10.573  21.978  -8.339  0.00  0.00      H
ATOM   1227  HE2 HIS   9      11.304  23.665  -6.498  1.00  0.00      H
ATOM   1228  N   LEU  10      16.386  21.410  -5.303  0.00  0.00      N
ATOM   1229  CA  LEU  10      16.451  22.245  -4.049  0.00  0.00      C
ATOM   1230  C   LEU  10      17.855  22.700  -3.558  0.00  0.00      C
ATOM   1231  O   LEU  10      18.024  23.830  -3.104  0.00  0.00      O
ATOM   1232  CB  LEU  10      15.562  21.628  -2.938  0.00  0.00      C
ATOM   1233  CG  LEU  10      14.037  21.642  -3.222  0.00  0.00      C
ATOM   1234  CD1 LEU  10      13.272  20.932  -2.099  0.00  0.00      C
ATOM   1235  CD2 LEU  10      13.444  23.061  -3.361  0.00  0.00      C
ATOM   1236  H   LEU  10      16.718  20.427  -5.418  0.00  0.00      H
ATOM   1237  HA  LEU  10      16.006  23.226  -4.274  0.00  0.00      H
ATOM   1238 1HB  LEU  10      15.896  20.589  -2.745  0.00  0.00      H
ATOM   1239 2HB  LEU  10      15.743  22.157  -1.981  0.00  0.00      H
ATOM   1240  HG  LEU  10      13.881  21.067  -4.157  0.00  0.00      H
ATOM   1241 1HD1 LEU  10      13.649  19.910  -1.920  0.00  0.00      H
ATOM   1242 2HD1 LEU  10      13.346  21.472  -1.137  0.00  0.00      H
ATOM   1243 3HD1 LEU  10      12.196  20.833  -2.338  0.00  0.00      H
ATOM   1244 1HD2 LEU  10      13.592  23.663  -2.444  0.00  0.00      H
ATOM   1245 2HD2 LEU  10      13.887  23.643  -4.188  0.00  0.00      H
ATOM   1246 3HD2 LEU  10      12.354  23.035  -3.555  0.00  0.00      H
ATOM   1247  N   GLU  11      18.880  21.879  -3.779  0.00  0.00      N
ATOM   1248  CA  GLU  11      20.245  22.318  -4.082  0.00  0.00      C
```

FIG. 8 - 38

```
ATOM   1249  C   GLU  11      20.493  23.583  -4.964  0.00  0.00           C
ATOM   1250  O   GLU  11      21.467  24.316  -4.792  0.00  0.00           O
ATOM   1251  CB  GLU  11      20.791  21.037  -4.731  0.00  0.00           C
ATOM   1252  CG  GLU  11      21.444  19.943  -3.873  0.00  0.00           C
ATOM   1253  CD  GLU  11      22.001  18.769  -4.686  0.00  0.00           C
ATOM   1254  OE1 GLU  11      22.176  18.803  -5.906  0.00  0.00           O
ATOM   1255  OE2 GLU  11      22.273  17.688  -3.903  0.00  0.00           O
ATOM   1256  H   GLU  11      18.702  20.866  -3.734  1.00  0.00           H
ATOM   1257  HA  GLU  11      20.786  22.441  -3.184  0.00  0.00           H
ATOM   1258  1HB GLU  11      20.036  20.569  -5.334  0.00  0.00           H
ATOM   1259  2HB GLU  11      21.465  21.324  -5.500  0.00  0.00           H
ATOM   1260  1HG GLU  11      22.246  20.392  -3.277  0.00  0.00           H
ATOM   1261  2HG GLU  11      20.692  19.573  -3.160  0.00  0.00           H
ATOM   1262  HE2 GLU  11      22.616  16.958  -4.419  0.00  0.00           H
ATOM   1263  N   HIS  12      19.663  23.745  -5.997  0.00  0.00           N
ATOM   1264  CA  HIS  12      19.795  24.738  -7.034  0.00  0.00           C
ATOM   1265  C   HIS  12      18.371  25.312  -7.326  0.00  0.00           C
ATOM   1266  O   HIS  12      17.772  25.069  -8.374  0.00  0.00           O
ATOM   1267  CB  HIS  12      20.393  23.956  -8.187  0.00  0.00           C
ATOM   1268  CG  HIS  12      21.692  23.137  -8.104  0.00  0.00           C
ATOM   1269  ND1 HIS  12      21.700  21.763  -8.263  0.00  0.00           N
ATOM   1270  CD2 HIS  12      22.952  23.581  -7.658  0.00  0.00           C
ATOM   1271  CE1 HIS  12      22.977  21.459  -7.857  0.00  0.00           C
ATOM   1272  NE2 HIS  12      23.812  22.493  -7.510  0.00  0.00           N
ATOM   1273  H   HIS  12      19.001  23.031  -6.247  0.00  0.00           H
ATOM   1274  HA  HIS  12      20.477  25.537  -6.812  0.00  0.00           H
ATOM   1275  1HB HIS  12      19.564  23.416  -8.609  0.00  0.00           H
ATOM   1276  2HB HIS  12      20.513  24.720  -8.897  0.00  0.00           H
ATOM   1277  HD1 HIS  12      20.876  21.151  -8.337  0.00  0.00           H
ATOM   1278  HD2 HIS  12      23.163  24.601  -7.346  0.00  0.00           H
ATOM   1279  HE1 HIS  12      23.276  20.421  -7.691  0.00  0.00           H
ATOM   1280  HE2 HIS  12      24.800  22.470  -7.220  1.00  0.00           H
ATOM   1281  N   SER  13      17.775  25.970  -6.339  0.00  0.00           N
ATOM   1282  CA  SER  13      16.348  26.376  -6.377  0.00  0.00           C
```

FIG. 8 - 39

```
ATOM   1283  C   SER  13      15.968  27.531  -7.346  0.00  0.00      C
ATOM   1284  O   SER  13      14.904  27.518  -7.963  0.00  0.00      O
ATOM   1285  CB  SER  13      15.834  26.584  -4.933  0.00  0.00      C
ATOM   1286  OG  SER  13      16.463  27.697  -4.292  0.00  0.00      O
ATOM   1287  H   SER  13      18.132  25.566  -5.494  0.00  0.00      H
ATOM   1288  HA  SER  13      15.872  25.484  -6.786  0.00  0.00      H
ATOM   1289 1HB  SER  13      14.735  26.724  -4.927  0.00  0.00      H
ATOM   1290 2HB  SER  13      16.011  25.676  -4.323  0.00  0.00      H
ATOM   1291  HG  SER  13      16.095  28.512  -4.653  0.00  0.00      H
ATOM   1292  N   ASN  14      16.947  28.406  -7.567  0.00  0.00      N
ATOM   1293  CA  ASN  14      17.176  29.086  -8.873  0.00  0.00      C
ATOM   1294  C   ASN  14      16.881  28.323 -10.193  0.00  0.00      C
ATOM   1295  O   ASN  14      16.213  28.825 -11.097  0.00  0.00      O
ATOM   1296  CB  ASN  14      18.619  29.676  -8.881  0.00  0.00      C
ATOM   1297  CG  ASN  14      19.834  28.729  -8.942  0.00  0.00      C
ATOM   1298  OD1 ASN  14      20.154  28.014  -8.001  0.00  0.00      O
ATOM   1299  ND2 ASN  14      20.541  28.643 -10.046  0.00  0.00      N
ATOM   1300  H   ASN  14      17.724  27.985  -7.044  0.00  0.00      H
ATOM   1301  HA  ASN  14      16.470  29.917  -8.909  0.00  0.00      H
ATOM   1302 1HB  ASN  14      18.681  30.384  -9.726  0.00  0.00      H
ATOM   1303 2HB  ASN  14      18.752  30.292  -7.978  0.00  0.00      H
ATOM   1304 1HD2 ASN  14      21.409  28.123  -9.897  0.00  0.00      H
ATOM   1305 2HD2 ASN  14      20.018  28.675 -10.935  0.00  0.00      H
ATOM   1306  N   LEU  15      17.450  27.127 -10.306  0.00  0.00      N
ATOM   1307  CA  LEU  15      17.465  26.335 -11.512  0.00  0.00      C
ATOM   1308  C   LEU  15      16.251  25.338 -11.667  0.00  0.00      C
ATOM   1309  O   LEU  15      16.055  24.796 -12.757  0.00  0.00      O
ATOM   1310  CB  LEU  15      18.924  25.801 -11.283  0.00  0.00      C
ATOM   1311  CG  LEU  15      19.360  24.759 -12.261  0.00  0.00      C
ATOM   1312  CD1 LEU  15      19.494  25.432 -13.633  0.00  0.00      C
ATOM   1313  CD2 LEU  15      20.669  24.037 -11.901  0.00  0.00      C
ATOM   1314  H   LEU  15      17.907  26.626  -9.528  0.00  0.00      H
ATOM   1315  HA  LEU  15      17.444  26.993 -12.402  0.00  0.00      H
ATOM   1316 1HB  LEU  15      19.670  26.615 -11.317  0.00  0.00      H
```

FIG. 8 - 40

```
ATOM   1317 2HB  LEU    15      19.045  25.327 -10.298  0.00  0.00           H
ATOM   1318  HG  LEU    15      18.495  24.107 -12.090  0.00  0.00           H
ATOM   1319 1HD1 LEU    15      20.218  26.273 -13.583  0.00  0.00           H
ATOM   1320 2HD1 LEU    15      19.835  24.737 -14.410  0.00  0.00           H
ATOM   1321 3HD1 LEU    15      18.538  25.874 -13.969  0.00  0.00           H
ATOM   1322 1HD2 LEU    15      21.520  24.740 -11.808  0.00  0.00           H
ATOM   1323 2HD2 LEU    15      20.588  23.472 -10.959  0.00  0.00           H
ATOM   1324 3HD2 LEU    15      20.947  23.302 -12.682  0.00  0.00           H
ATOM   1325  N   CYS    16      15.419  25.107 -10.630  0.00  0.00           N
ATOM   1326  CA  CYS    16      13.995  24.752 -10.839  0.00  0.00           C
ATOM   1327  C   CYS    16      13.006  25.959 -10.966  0.00  0.00           C
ATOM   1328  O   CYS    16      12.157  25.980 -11.850  0.00  0.00           O
ATOM   1329  CB  CYS    16      13.583  23.811  -9.701  0.00  0.00           C
ATOM   1330  SG  CYS    16      12.114  22.898 -10.210  0.00  0.00           S
ATOM   1331  H   CYS    16      15.717  25.614  -9.788  0.00  0.00           H
ATOM   1332  HA  CYS    16      13.901  24.193 -11.786  0.00  0.00           H
ATOM   1333 1HB  CYS    16      14.291  23.004  -9.495  0.00  0.00           H
ATOM   1334 2HB  CYS    16      13.513  24.383  -8.752  0.00  0.00           H
TER    1335      CYS    16
HETATM 1336  N   NH2    17H     13.003  26.957 -10.100  0.00  0.00           N
HETATM 1337 1HN  NH2    17H     12.396  27.730 -10.391  0.00  0.00           H
HETATM 1338 2HN  NH2    17H     13.772  26.998  -9.412  0.00  0.00           H
ENDMDL
MODEL      7
ATOM   1339  N   GLY     1      15.155  24.544 -15.190  0.00  0.00           N
ATOM   1340  CA  GLY     1      15.819  23.221 -15.430  0.00  0.00           C
ATOM   1341  C   GLY     1      15.274  22.088 -14.544  0.00  0.00           C
ATOM   1342  O   GLY     1      14.062  21.875 -14.577  0.00  0.00           O
ATOM   1343  1H  GLY     1      15.295  24.827 -14.210  1.00  0.00           H
ATOM   1344  2H  GLY     1      15.566  25.253 -15.814  1.00  0.00           H
ATOM   1345  3H  GLY     1      14.146  24.462 -15.383  1.00  0.00           H
ATOM   1346  1HA GLY     1      15.658  22.889 -16.472  0.00  0.00           H
ATOM   1347  2HA GLY     1      16.912  23.301 -15.283  0.00  0.00           H
ATOM   1348  N   CYS     2      16.114  21.366 -13.767  0.00  0.00           N
```

FIG. 8 - 41

```
ATOM   1349  CA  CYS     2      15.626  20.295 -12.909  0.00  0.00           C
ATOM   1350  C   CYS     2      14.792  20.665 -11.648  0.00  0.00           C
ATOM   1351  O   CYS     2      15.215  20.910 -10.526  0.00  0.00           O
ATOM   1352  CB  CYS     2      16.751  19.310 -12.674  0.00  0.00           C
ATOM   1353  SG  CYS     2      17.644  19.532 -11.107  0.00  0.00           S
ATOM   1354  H   CYS     2      16.824  20.853 -14.280  0.00  0.00           H
ATOM   1355  HA  CYS     2      14.997  19.697 -13.613  0.00  0.00           H
ATOM   1356  1HB CYS     2      16.137  18.416 -12.647  0.00  0.00           H
ATOM   1357  2HB CYS     2      17.428  19.169 -13.534  0.00  0.00           H
ATOM   1358  N   CYS     3      13.539  20.634 -11.987  0.00  0.00           N
ATOM   1359  CA  CYS     3      12.379  20.624 -11.063  0.00  0.00           C
ATOM   1360  C   CYS     3      11.834  19.220 -10.613  0.00  0.00           C
ATOM   1361  O   CYS     3      11.402  19.067  -9.471  0.00  0.00           O
ATOM   1362  CB  CYS     3      11.278  21.375 -11.838  0.00  0.00           C
ATOM   1363  SG  CYS     3      11.556  23.161 -11.884  0.00  0.00           S
ATOM   1364  H   CYS     3      13.660  20.271 -12.944  0.00  0.00           H
ATOM   1365  HA  CYS     3      12.642  21.191 -10.135  0.00  0.00           H
ATOM   1366  1HB CYS     3      11.177  21.011 -12.881  0.00  0.00           H
ATOM   1367  2HB CYS     3      10.295  21.142 -11.401  0.00  0.00           H
ATOM   1368  N   SER     4      11.798  18.233 -11.513  0.00  0.00           N
ATOM   1369  CA  SER     4      11.212  16.880 -11.284  0.00  0.00           C
ATOM   1370  C   SER     4      11.900  15.953 -10.226  0.00  0.00           C
ATOM   1371  O   SER     4      11.291  15.001  -9.737  0.00  0.00           O
ATOM   1372  CB  SER     4      11.102  16.202 -12.653  0.00  0.00           C
ATOM   1373  OG  SER     4      10.313  16.945 -13.588  0.00  0.00           O
ATOM   1374  H   SER     4      12.257  18.450 -12.384  0.00  0.00           H
ATOM   1375  HA  SER     4      10.171  16.982 -10.986  0.00  0.00           H
ATOM   1376  1HB SER     4      12.112  16.058 -13.027  0.00  0.00           H
ATOM   1377  2HB SER     4      10.676  15.192 -12.534  0.00  0.00           H
ATOM   1378  HG  SER     4       9.989  16.329 -14.257  0.00  0.00           H
ATOM   1379  N   ASN     5      13.126  16.294  -9.806  0.00  0.00           N
ATOM   1380  CA  ASN     5      13.766  15.691  -8.624  0.00  0.00           C
ATOM   1381  C   ASN     5      13.379  16.460  -7.309  0.00  0.00           C
ATOM   1382  O   ASN     5      13.321  17.696  -7.339  0.00  0.00           O
```

FIG. 8 - 42

```
ATOM   1383  CB  ASN     5      15.296  15.867  -8.797  0.00  0.00           C
ATOM   1384  CG  ASN     5      15.978  15.043  -9.867  0.00  0.00           C
ATOM   1385  OD1 ASN     5      16.076  15.412 -11.030  0.00  0.00           O
ATOM   1386  ND2 ASN     5      16.554  13.958  -9.443  0.00  0.00           N
ATOM   1387  H   ASN     5      13.581  17.005 -10.386  0.00  0.00           H
ATOM   1388  HA  ASN     5      13.509  14.617  -8.561  0.00  0.00           H
ATOM   1389 1HB  ASN     5      15.586  16.928  -8.913  0.00  0.00           H
ATOM   1390 2HB  ASN     5      15.776  15.600  -7.857  0.00  0.00           H
ATOM   1391 1HD2 ASN     5      17.207  13.570 -10.115  0.00  0.00           H
ATOM   1392 2HD2 ASN     5      16.566  13.873  -8.424  0.00  0.00           H
ATOM   1393  N   PRO     6      13.248  15.824  -6.111  0.00  0.00           N
ATOM   1394  CA  PRO     6      13.315  16.565  -4.810  0.00  0.00           C
ATOM   1395  C   PRO     6      14.632  17.365  -4.542  0.00  0.00           C
ATOM   1396  O   PRO     6      14.643  18.566  -4.276  0.00  0.00           O
ATOM   1397  CB  PRO     6      13.030  15.433  -3.802  0.00  0.00           C
ATOM   1398  CG  PRO     6      13.620  14.193  -4.479  0.00  0.00           C
ATOM   1399  CD  PRO     6      13.228  14.352  -5.944  0.00  0.00           C
ATOM   1400  HA  PRO     6      12.514  17.299  -4.753  0.00  0.00           H
ATOM   1401 1HB  PRO     6      13.454  15.627  -2.798  0.00  0.00           H
ATOM   1402 2HB  PRO     6      11.937  15.311  -3.658  0.00  0.00           H
ATOM   1403 1HG  PRO     6      14.716  14.152  -4.376  0.00  0.00           H
ATOM   1404 2HG  PRO     6      13.289  13.257  -4.036  0.00  0.00           H
ATOM   1405 1HD  PRO     6      13.915  13.793  -6.597  0.00  0.00           H
ATOM   1406 2HD  PRO     6      12.222  13.946  -6.148  0.00  0.00           H
ATOM   1407  N   VAL     7      15.742  16.658  -4.688  0.00  0.00           N
ATOM   1408  CA  VAL     7      17.093  17.079  -4.256  0.00  0.00           C
ATOM   1409  C   VAL     7      17.730  18.083  -5.231  0.00  0.00           C
ATOM   1410  O   VAL     7      18.088  19.193  -4.834  0.00  0.00           O
ATOM   1411  CB  VAL     7      17.886  15.728  -4.112  0.00  0.00           C
ATOM   1412  CG1 VAL     7      19.409  15.878  -3.946  0.00  0.00           C
ATOM   1413  CG2 VAL     7      17.422  14.872  -2.921  0.00  0.00           C
ATOM   1414  H   VAL     7      15.531  15.687  -4.926  0.00  0.00           H
ATOM   1415  HA  VAL     7      17.024  17.649  -3.310  0.00  0.00           H
ATOM   1416  HB  VAL     7      17.713  15.129  -5.039  0.00  0.00           H
```

FIG. 8 - 43

```
ATOM   1417  1HG1 VAL   7      19.659  16.478  -3.051  0.00  0.00           H
ATOM   1418  2HG1 VAL   7      19.905  14.895  -3.844  0.00  0.00           H
ATOM   1419  3HG1 VAL   7      19.867  16.371  -4.822  0.00  0.00           H
ATOM   1420  1HG2 VAL   7      16.339  14.674  -2.956  0.00  0.00           H
ATOM   1421  2HG2 VAL   7      17.926  13.887  -2.917  0.00  0.00           H
ATOM   1422  3HG2 VAL   7      17.631  15.375  -1.960  0.00  0.00           H
ATOM   1423  N    CYS   8      17.876  17.700  -6.509  0.00  0.00           N
ATOM   1424  CA   CYS   8      18.484  18.600  -7.528  0.00  0.00           C
ATOM   1425  C    CYS   8      17.786  19.937  -7.876  0.00  0.00           C
ATOM   1426  O    CYS   8      18.420  20.950  -8.184  0.00  0.00           O
ATOM   1427  CB   CYS   8      19.013  17.847  -8.772  0.00  0.00           C
ATOM   1428  SG   CYS   8      17.768  17.790 -10.095  0.00  0.00           S
ATOM   1429  H    CYS   8      17.543  16.742  -6.603  0.00  0.00           H
ATOM   1430  HA   CYS   8      19.291  18.993  -6.930  0.00  0.00           H
ATOM   1431  1HB  CYS   8      19.906  18.359  -9.176  0.00  0.00           H
ATOM   1432  2HB  CYS   8      19.346  16.820  -8.529  0.00  0.00           H
ATOM   1433  N    HIS   9      16.477  19.926  -7.681  0.00  0.00           N
ATOM   1434  CA   HIS   9      15.651  21.129  -7.532  0.00  0.00           C
ATOM   1435  C    HIS   9      16.063  22.015  -6.330  0.00  0.00           C
ATOM   1436  O    HIS   9      16.098  23.228  -6.459  0.00  0.00           O
ATOM   1437  CB   HIS   9      14.198  20.586  -7.494  0.00  0.00           C
ATOM   1438  CG   HIS   9      12.943  21.249  -6.940  0.00  0.00           C
ATOM   1439  ND1  HIS   9      11.711  20.824  -7.379  0.00  0.00           N
ATOM   1440  CD2  HIS   9      12.831  22.562  -6.502  0.00  0.00           C
ATOM   1441  CE1  HIS   9      10.992  21.982  -7.327  0.00  0.00           C
ATOM   1442  NE2  HIS   9      11.553  23.063  -6.710  0.00  0.00           N
ATOM   1443  H    HIS   9      16.155  19.012  -7.380  0.00  0.00           H
ATOM   1444  HA   HIS   9      15.802  21.717  -8.414  0.00  0.00           H
ATOM   1445  1HB  HIS   9      13.998  20.013  -8.412  0.00  0.00           H
ATOM   1446  2HB  HIS   9      14.275  19.844  -6.679  0.00  0.00           H
ATOM   1447  HD1  HIS   9      11.523  19.983  -7.958  0.00  0.00           H
ATOM   1448  HD2  HIS   9      13.710  23.124  -6.297  0.00  0.00           H
ATOM   1449  HE1  HIS   9      10.240  22.154  -8.091  0.00  0.00           H
ATOM   1450  HE2  HIS   9      11.149  23.979  -6.470  1.00  0.00           H
```

FIG. 8 - 44

```
ATOM   1451  N   LEU  10      16.266  21.423  -5.162  0.00  0.00           N
ATOM   1452  CA  LEU  10      16.336  22.200  -3.872  0.00  0.00           C
ATOM   1453  C   LEU  10      17.740  22.697  -3.410  0.00  0.00           C
ATOM   1454  O   LEU  10      17.901  23.851  -3.008  0.00  0.00           O
ATOM   1455  CB  LEU  10      15.445  21.515  -2.803  0.00  0.00           C
ATOM   1456  CG  LEU  10      13.921  21.539  -3.121  0.00  0.00           C
ATOM   1457  CD1 LEU  10      13.144  20.672  -2.128  0.00  0.00           C
ATOM   1458  CD2 LEU  10      13.306  22.955  -3.130  0.00  0.00           C
ATOM   1459  H   LEU  10      16.565  20.437  -5.352  0.00  0.00           H
ATOM   1460  HA  LEU  10      15.853  23.177  -4.037  0.00  0.00           H
ATOM   1461  1HB LEU  10      15.789  20.470  -2.670  0.00  0.00           H
ATOM   1462  2HB LEU  10      15.614  21.988  -1.817  0.00  0.00           H
ATOM   1463  HG  LEU  10      13.776  21.078  -4.117  0.00  0.00           H
ATOM   1464  1HD1 LEU  10     13.514  19.631  -2.128  0.00  0.00           H
ATOM   1465  2HD1 LEU  10     13.219  21.053  -1.094  0.00  0.00           H
ATOM   1466  3HD1 LEU  10     12.070  20.622  -2.390  0.00  0.00           H
ATOM   1467  1HD2 LEU  10     13.431  23.469  -2.159  0.00  0.00           H
ATOM   1468  2HD2 LEU  10     13.750  23.615  -3.895  0.00  0.00           H
ATOM   1469  3HD2 LEU  10     12.221  22.930  -3.347  0.00  0.00           H
ATOM   1470  N   GLU  11      18.774  21.884  -3.619  0.00  0.00           N
ATOM   1471  CA  GLU  11      20.172  22.330  -3.801  0.00  0.00           C
ATOM   1472  C   GLU  11      20.470  23.502  -4.793  0.00  0.00           C
ATOM   1473  O   GLU  11      21.407  24.281  -4.611  0.00  0.00           O
ATOM   1474  CB  GLU  11      20.839  21.016  -4.293  0.00  0.00           C
ATOM   1475  CG  GLU  11      21.326  20.027  -3.212  0.00  0.00           C
ATOM   1476  CD  GLU  11      22.604  20.452  -2.487  0.00  0.00           C
ATOM   1477  OE1 GLU  11      23.633  20.783  -3.070  0.00  0.00           O
ATOM   1478  OE2 GLU  11      22.472  20.422  -1.136  0.00  0.00           O
ATOM   1479  H   GLU  11      18.586  20.872  -3.656  1.00  0.00           H
ATOM   1480  HA  GLU  11      20.610  22.632  -2.848  0.00  0.00           H
ATOM   1481  1HB GLU  11      20.226  20.477  -5.044  0.00  0.00           H
ATOM   1482  2HB GLU  11      21.686  21.315  -4.886  0.00  0.00           H
ATOM   1483  1HG GLU  11      20.504  19.866  -2.496  0.00  0.00           H
ATOM   1484  2HG GLU  11      21.522  19.037  -3.661  0.00  0.00           H
```

FIG. 8-44

FIG. 8 - 45

```
ATOM   1485  HE2 GLU  11      23.298  20.695  -0.733  0.00  0.00           H
ATOM   1486  N   HIS  12      19.735  23.535  -5.906  0.00  0.00           N
ATOM   1487  CA  HIS  12      19.922  24.514  -6.991  0.00  0.00           C
ATOM   1488  C   HIS  12      18.521  25.072  -7.409  0.00  0.00           C
ATOM   1489  O   HIS  12      17.989  24.766  -8.472  0.00  0.00           O
ATOM   1490  CB  HIS  12      20.755  23.800  -8.086  0.00  0.00           C
ATOM   1491  CG  HIS  12      22.215  23.450  -7.743  0.00  0.00           C
ATOM   1492  ND1 HIS  12      22.673  22.147  -7.631  0.00  0.00           N
ATOM   1493  CD2 HIS  12      23.219  24.344  -7.309  0.00  0.00           C
ATOM   1494  CE1 HIS  12      23.923  22.348  -7.094  0.00  0.00           C
ATOM   1495  NE2 HIS  12      24.346  23.637  -6.897  0.00  0.00           N
ATOM   1496  H   HIS  12      18.881  22.984  -5.810  0.00  0.00           H
ATOM   1497  HA  HIS  12      20.503  25.381  -6.649  0.00  0.00           H
ATOM   1498  1HB HIS  12      20.193  22.896  -8.379  0.00  0.00           H
ATOM   1499  2HB HIS  12      20.761  24.433  -8.980  0.00  0.00           H
ATOM   1500  HD1 HIS  12      22.161  21.270  -7.782  0.00  0.00           H
ATOM   1501  HD2 HIS  12      23.080  25.414  -7.199  0.00  0.00           H
ATOM   1502  HE1 HIS  12      24.546  21.507  -6.783  0.00  0.00           H
ATOM   1503  HE2 HIS  12      25.247  23.986  -6.541  1.00  0.00           H
ATOM   1504  N   SER  13      17.921  25.863  -6.509  0.00  0.00           N
ATOM   1505  CA  SER  13      16.491  26.279  -6.562  0.00  0.00           C
ATOM   1506  C   SER  13      16.009  27.341  -7.576  0.00  0.00           C
ATOM   1507  O   SER  13      14.955  27.195  -8.200  0.00  0.00           O
ATOM   1508  CB  SER  13      16.013  26.552  -5.115  0.00  0.00           C
ATOM   1509  OG  SER  13      16.675  27.694  -4.563  0.00  0.00           O
ATOM   1510  H   SER  13      18.213  25.528  -5.602  0.00  0.00           H
ATOM   1511  HA  SER  13      15.984  25.406  -6.930  0.00  0.00           H
ATOM   1512  1HB SER  13      14.918  26.716  -5.099  0.00  0.00           H
ATOM   1513  2HB SER  13      16.189  25.669  -4.468  0.00  0.00           H
ATOM   1514  HG  SER  13      16.292  27.883  -3.697  0.00  0.00           H
ATOM   1515  N   ASN  14      16.887  28.295  -7.830  0.00  0.00           N
ATOM   1516  CA  ASN  14      16.931  29.039  -9.130  0.00  0.00           C
ATOM   1517  C   ASN  14      16.988  28.153 -10.428  0.00  0.00           C
ATOM   1518  O   ASN  14      16.420  28.498 -11.464  0.00  0.00           O
```

FIG. 8 - 46

```
ATOM   1519  CB  ASN  14      18.123  30.038  -9.133  0.00  0.00      C
ATOM   1520  CG  ASN  14      18.129  31.105  -8.037  0.00  0.00      C
ATOM   1521  OD1 ASN  14      17.144  31.781  -7.777  0.00  0.00      O
ATOM   1522  ND2 ASN  14      19.237  31.299  -7.371  0.00  0.00      N
ATOM   1523  H   ASN  14      17.682  28.043  -7.236  0.00  0.00      H
ATOM   1524  HA  ASN  14      15.996  29.614  -9.211  0.00  0.00      H
ATOM   1525  1HB ASN  14      19.077  29.480  -9.141  0.00  0.00      H
ATOM   1526  2HB ASN  14      18.117  30.598 -10.086  0.00  0.00      H
ATOM   1527  1HD2 ASN  14     19.181  32.098  -6.730  0.00  0.00      H
ATOM   1528  2HD2 ASN  14     20.070  30.813  -7.710  0.00  0.00      H
ATOM   1529  N   LEU  15      17.672  27.002 -10.353  0.00  0.00      N
ATOM   1530  CA  LEU  15      17.873  26.068 -11.480  0.00  0.00      C
ATOM   1531  C   LEU  15      16.774  24.953 -11.639  0.00  0.00      C
ATOM   1532  O   LEU  15      16.617  24.441 -12.747  0.00  0.00      O
ATOM   1533  CB  LEU  15      19.339  25.555 -11.398  0.00  0.00      C
ATOM   1534  CG  LEU  15      20.437  26.670 -11.332  0.00  0.00      C
ATOM   1535  CD1 LEU  15      20.934  27.055  -9.923  0.00  0.00      C
ATOM   1536  CD2 LEU  15      21.647  26.316 -12.197  0.00  0.00      C
ATOM   1537  H   LEU  15      18.075  26.786  -9.437  0.00  0.00      H
ATOM   1538  HA  LEU  15      17.817  26.655 -12.415  0.00  0.00      H
ATOM   1539  1HB LEU  15      19.441  24.839 -10.569  0.00  0.00      H
ATOM   1540  2HB LEU  15      19.501  24.930 -12.297  0.00  0.00      H
ATOM   1541  HG  LEU  15      19.973  27.590 -11.738  0.00  0.00      H
ATOM   1542  1HD1 LEU  15     20.114  27.186  -9.195  0.00  0.00      H
ATOM   1543  2HD1 LEU  15     21.652  26.334  -9.501  0.00  0.00      H
ATOM   1544  3HD1 LEU  15     21.466  28.028  -9.953  0.00  0.00      H
ATOM   1545  1HD2 LEU  15     21.352  26.151 -13.249  0.00  0.00      H
ATOM   1546  2HD2 LEU  15     22.393  27.132 -12.201  0.00  0.00      H
ATOM   1547  3HD2 LEU  15     22.152  25.399 -11.842  0.00  0.00      H
ATOM   1548  N   CYS  16      15.902  24.687 -10.637  0.00  0.00      N
ATOM   1549  CA  CYS  16      14.447  24.472 -10.924  0.00  0.00      C
ATOM   1550  C   CYS  16      13.798  25.765 -11.533  0.00  0.00      C
ATOM   1551  O   CYS  16      13.518  25.816 -12.729  0.00  0.00      O
ATOM   1552  CB  CYS  16      13.661  23.955  -9.687  0.00  0.00      C
```

FIG. 8 - 47

```
ATOM   1553  SG  CYS    16      11.886  23.916 -10.051  0.00  0.00           S
ATOM   1554  H   CYS    16      16.215  25.198  -9.796  0.00  0.00           H
ATOM   1555  HA  CYS    16      14.354  23.684 -11.698  0.00  0.00           H
ATOM   1556 1HB  CYS    16      13.919  22.928  -9.378  0.00  0.00           H
ATOM   1557 2HB  CYS    16      13.846  24.608  -8.812  0.00  0.00           H
TER    1558      CYS    16
HETATM 1559  N   NH2    17H     13.607  26.834 -10.777  0.00  0.00           N
HETATM 1560 1HN  NH2    17H     13.331  27.672 -11.299  0.00  0.00           H
HETATM 1561 2HN  NH2    17H     14.065  26.808  -9.844  0.00  0.00           H
ENDMDL
MODEL        8
ATOM   1562  N   GLY     1      15.059  13.097 -14.332  0.00  0.00           N
ATOM   1563  CA  GLY     1      15.949  14.309 -14.317  0.00  0.00           C
ATOM   1564  C   GLY     1      16.291  14.867 -12.909  0.00  0.00           C
ATOM   1565  O   GLY     1      15.714  14.437 -11.915  0.00  0.00           O
ATOM   1566 1H   GLY     1      15.514  12.330 -13.817  1.00  0.00           H
ATOM   1567 2H   GLY     1      14.160  13.325 -13.883  1.00  0.00           H
ATOM   1568 3H   GLY     1      14.892  12.806 -15.306  1.00  0.00           H
ATOM   1569 1HA  GLY     1      16.900  14.089 -14.841  0.00  0.00           H
ATOM   1570 2HA  GLY     1      15.485  15.135 -14.893  0.00  0.00           H
ATOM   1571  N   CYS     2      17.213  15.836 -12.811  0.00  0.00           N
ATOM   1572  CA  CYS     2      17.832  16.210 -11.496  0.00  0.00           C
ATOM   1573  C   CYS     2      17.006  17.347 -10.772  0.00  0.00           C
ATOM   1574  O   CYS     2      16.538  17.131  -9.659  0.00  0.00           O
ATOM   1575  CB  CYS     2      19.321  16.437 -11.885  0.00  0.00           C
ATOM   1576  SG  CYS     2      20.425  17.454 -10.867  0.00  0.00           S
ATOM   1577  H   CYS     2      17.770  15.985 -13.661  0.00  0.00           H
ATOM   1578  HA  CYS     2      17.823  15.346 -10.798  0.00  0.00           H
ATOM   1579 1HB  CYS     2      19.820  15.480 -12.128  0.00  0.00           H
ATOM   1580 2HB  CYS     2      19.337  17.030 -12.824  0.00  0.00           H
ATOM   1581  N   CYS     3      16.700  18.500 -11.400  0.00  0.00           N
ATOM   1582  CA  CYS     3      15.475  19.311 -11.108  0.00  0.00           C
ATOM   1583  C   CYS     3      14.057  18.627 -11.218  0.00  0.00           C
ATOM   1584  O   CYS     3      13.104  19.118 -10.607  0.00  0.00           O
```

FIG. 8 - 48

```
ATOM   1585  CB  CYS     3      15.714  20.442 -12.118  0.00  0.00           C
ATOM   1586  SG  CYS     3      16.874  21.609 -11.379  0.00  0.00           S
ATOM   1587  H   CYS     3      17.037  18.582 -12.364  0.00  0.00           H
ATOM   1588  HA  CYS     3      15.467  19.806 -10.100  0.00  0.00           H
ATOM   1589 1HB  CYS     3      16.043  20.132 -13.133  0.00  0.00           H
ATOM   1590 2HB  CYS     3      14.777  20.947 -12.316  0.00  0.00           H
ATOM   1591  N   SER     4      13.926  17.499 -11.937  0.00  0.00           N
ATOM   1592  CA  SER     4      12.776  16.552 -11.773  0.00  0.00           C
ATOM   1593  C   SER     4      12.750  15.630 -10.495  0.00  0.00           C
ATOM   1594  O   SER     4      11.677  15.133 -10.148  0.00  0.00           O
ATOM   1595  CB  SER     4      12.567  15.841 -13.121  0.00  0.00           C
ATOM   1596  OG  SER     4      11.800  14.639 -13.029  0.00  0.00           O
ATOM   1597  H   SER     4      14.830  17.182 -12.295  0.00  0.00           H
ATOM   1598  HA  SER     4      11.864  17.140 -11.695  0.00  0.00           H
ATOM   1599 1HB  SER     4      12.092  16.532 -13.848  0.00  0.00           H
ATOM   1600 2HB  SER     4      13.537  15.611 -13.545  0.00  0.00           H
ATOM   1601  HG  SER     4      11.077  14.794 -12.402  0.00  0.00           H
ATOM   1602  N   ASN     5      13.854  15.481  -9.746  0.00  0.00           N
ATOM   1603  CA  ASN     5      13.825  15.066  -8.328  0.00  0.00           C
ATOM   1604  C   ASN     5      13.679  16.328  -7.403  0.00  0.00           C
ATOM   1605  O   ASN     5      14.295  17.363  -7.698  0.00  0.00           O
ATOM   1606  CB  ASN     5      15.213  14.467  -7.982  0.00  0.00           C
ATOM   1607  CG  ASN     5      15.604  13.090  -8.478  0.00  0.00           C
ATOM   1608  OD1 ASN     5      15.111  12.523  -9.443  0.00  0.00           O
ATOM   1609  ND2 ASN     5      16.541  12.529  -7.764  0.00  0.00           N
ATOM   1610  H   ASN     5      14.730  15.832 -10.131  0.00  0.00           H
ATOM   1611  HA  ASN     5      13.009  14.339  -8.127  0.00  0.00           H
ATOM   1612 1HB  ASN     5      16.026  15.166  -8.249  0.00  0.00           H
ATOM   1613 2HB  ASN     5      15.262  14.397  -6.889  0.00  0.00           H
ATOM   1614 1HD2 ASN     5      16.559  11.520  -7.892  0.00  0.00           H
ATOM   1615 2HD2 ASN     5      16.775  13.053  -6.910  0.00  0.00           H
ATOM   1616  N   PRO     6      12.997  16.274  -6.225  0.00  0.00           N
ATOM   1617  CA  PRO     6      12.988  17.412  -5.263  0.00  0.00           C
ATOM   1618  C   PRO     6      14.359  17.956  -4.757  0.00  0.00           C
```

FIG. 8 - 49

```
ATOM   1619  O   PRO   6      14.585  19.158  -4.734  0.00  0.00           O
ATOM   1620  CB  PRO   6      11.993  16.949  -4.189  0.00  0.00           C
ATOM   1621  CG  PRO   6      11.829  15.445  -4.336  0.00  0.00           C
ATOM   1622  CD  PRO   6      12.277  15.077  -5.751  0.00  0.00           C
ATOM   1623  HA  PRO   6      12.543  18.273  -5.754  0.00  0.00           H
ATOM   1624  1HB PRO   6      12.289  17.264  -3.172  0.00  0.00           H
ATOM   1625  2HB PRO   6      11.000  17.378  -4.349  0.00  0.00           H
ATOM   1626  1HG PRO   6      12.454  14.982  -3.573  0.00  0.00           H
ATOM   1627  2HG PRO   6      10.806  15.099  -4.110  0.00  0.00           H
ATOM   1628  1HD PRO   6      12.903  14.170  -5.741  0.00  0.00           H
ATOM   1629  2HD PRO   6      11.442  14.834  -6.432  0.00  0.00           H
ATOM   1630  N   VAL   7      15.290  17.064  -4.458  0.00  0.00           N
ATOM   1631  CA  VAL   7      16.576  17.374  -3.758  0.00  0.00           C
ATOM   1632  C   VAL   7      17.714  17.925  -4.675  0.00  0.00           C
ATOM   1633  O   VAL   7      18.391  18.877  -4.320  0.00  0.00           O
ATOM   1634  CB  VAL   7      16.943  16.044  -2.997  0.00  0.00           C
ATOM   1635  CG1 VAL   7      18.350  16.028  -2.346  0.00  0.00           C
ATOM   1636  CG2 VAL   7      15.962  15.676  -1.854  0.00  0.00           C
ATOM   1637  H   VAL   7      14.934  16.119  -4.590  0.00  0.00           H
ATOM   1638  HA  VAL   7      16.393  18.231  -3.079  0.00  0.00           H
ATOM   1639  HB  VAL   7      16.901  15.227  -3.762  0.00  0.00           H
ATOM   1640  1HG1 VAL   7      19.160  16.214  -3.075  0.00  0.00           H
ATOM   1641  2HG1 VAL   7      18.453  16.795  -1.552  0.00  0.00           H
ATOM   1642  3HG1 VAL   7      18.584  15.052  -1.879  0.00  0.00           H
ATOM   1643  1HG2 VAL   7      14.920  15.564  -2.206  0.00  0.00           H
ATOM   1644  2HG2 VAL   7      16.225  14.716  -1.369  0.00  0.00           H
ATOM   1645  3HG2 VAL   7      15.944  16.442  -1.054  0.00  0.00           H
ATOM   1646  N   CYS   8      17.896  17.370  -5.866  0.00  0.00           N
ATOM   1647  CA  CYS   8      18.291  18.144  -7.057  0.00  0.00           C
ATOM   1648  C   CYS   8      17.820  19.591  -7.382  0.00  0.00           C
ATOM   1649  O   CYS   8      18.590  20.542  -7.483  0.00  0.00           O
ATOM   1650  CB  CYS   8      19.557  17.670  -7.794  0.00  0.00           C
ATOM   1651  SG  CYS   8      19.558  18.491  -9.413  0.00  0.00           S
ATOM   1652  H   CYS   8      17.159  16.662  -5.968  0.00  0.00           H
```

FIG. 8 - 50

```
ATOM   1653  HA  CYS   8      17.492  17.708  -7.595  0.00  0.00      H
ATOM   1654 1HB  CYS   8      20.468  17.938  -7.226  0.00  0.00      H
ATOM   1655 2HB  CYS   8      19.569  16.571  -7.922  0.00  0.00      H
ATOM   1656  N   HIS   9      16.514  19.732  -7.646  0.00  0.00      N
ATOM   1657  CA  HIS   9      15.806  21.026  -7.866  0.00  0.00      C
ATOM   1658  C   HIS   9      16.177  22.061  -6.771  0.00  0.00      C
ATOM   1659  O   HIS   9      16.500  23.214  -7.025  0.00  0.00      O
ATOM   1660  CB  HIS   9      14.312  20.632  -7.956  0.00  0.00      C
ATOM   1661  CG  HIS   9      13.007  21.391  -7.825  0.00  0.00      C
ATOM   1662  ND1 HIS   9      12.014  21.276  -8.780  0.00  0.00      N
ATOM   1663  CD2 HIS   9      12.941  22.618  -7.238  0.00  0.00      C
ATOM   1664  CE1 HIS   9      11.445  22.526  -8.711  0.00  0.00      C
ATOM   1665  NE2 HIS   9      11.913  23.392  -7.760  0.00  0.00      N
ATOM   1666  H   HIS   9      16.006  18.837  -7.624  0.00  0.00      H
ATOM   1667  HA  HIS   9      16.027  21.422  -8.827  0.00  0.00      H
ATOM   1668 1HB  HIS   9      14.187  19.622  -8.196  0.00  0.00      H
ATOM   1669 2HB  HIS   9      14.266  20.336  -6.918  0.00  0.00      H
ATOM   1670  HD1 HIS   9      11.954  20.579  -9.539  0.00  0.00      H
ATOM   1671  HD2 HIS   9      13.914  22.898  -6.925  0.00  0.00      H
ATOM   1672  HE1 HIS   9      10.845  22.914  -9.537  0.00  0.00      H
ATOM   1673  HE2 HIS   9      11.596  24.338  -7.506  1.00  0.00      H
ATOM   1674  N   LEU  10      16.090  21.515  -5.570  0.00  0.00      N
ATOM   1675  CA  LEU  10      16.401  22.225  -4.305  0.00  0.00      C
ATOM   1676  C   LEU  10      17.889  22.281  -3.854  0.00  0.00      C
ATOM   1677  O   LEU  10      18.229  23.109  -3.010  0.00  0.00      O
ATOM   1678  CB  LEU  10      15.379  21.786  -3.223  0.00  0.00      C
ATOM   1679  CG  LEU  10      13.872  22.022  -3.547  0.00  0.00      C
ATOM   1680  CD1 LEU  10      12.982  21.431  -2.453  0.00  0.00      C
ATOM   1681  CD2 LEU  10      13.529  23.504  -3.758  0.00  0.00      C
ATOM   1682  H   LEU  10      16.128  20.478  -5.801  0.00  0.00      H
ATOM   1683  HA  LEU  10      16.224  23.291  -4.483  0.00  0.00      H
ATOM   1684 1HB  LEU  10      15.550  20.715  -3.000  0.00  0.00      H
ATOM   1685 2HB  LEU  10      15.625  22.301  -2.275  0.00  0.00      H
ATOM   1686  HG  LEU  10      13.613  21.483  -4.477  0.00  0.00      H
```

FIG. 8 - 51

```
ATOM   1687 1HD1 LEU  10      13.181  21.885  -1.465  0.00  0.00           H
ATOM   1688 2HD1 LEU  10      11.909  21.579  -2.676  0.00  0.00           H
ATOM   1689 3HD1 LEU  10      13.138  20.340  -2.356  0.00  0.00           H
ATOM   1690 1HD2 LEU  10      13.834  24.128  -2.897  0.00  0.00           H
ATOM   1691 2HD2 LEU  10      14.034  23.922  -4.648  0.00  0.00           H
ATOM   1692 3HD2 LEU  10      12.448  23.672  -3.917  0.00  0.00           H
ATOM   1693  N   GLU  11      18.812  21.595  -4.546  0.00  0.00           N
ATOM   1694  CA  GLU  11      20.223  21.983  -4.645  0.00  0.00           C
ATOM   1695  C   GLU  11      20.517  23.347  -5.351  0.00  0.00           C
ATOM   1696  O   GLU  11      21.509  24.018  -5.079  0.00  0.00           O
ATOM   1697  CB  GLU  11      20.849  20.761  -5.350  0.00  0.00           C
ATOM   1698  CG  GLU  11      21.657  19.817  -4.467  0.00  0.00           C
ATOM   1699  CD  GLU  11      22.982  20.363  -3.944  0.00  0.00           C
ATOM   1700  OE1 GLU  11      23.932  20.633  -4.671  0.00  0.00           O
ATOM   1701  OE2 GLU  11      22.983  20.526  -2.595  0.00  0.00           O
ATOM   1702  H   GLU  11      18.511  20.743  -5.039  1.00  0.00           H
ATOM   1703  HA  GLU  11      20.630  22.007  -3.647  0.00  0.00           H
ATOM   1704 1HB  GLU  11      20.102  20.092  -5.750  0.00  0.00           H
ATOM   1705 2HB  GLU  11      21.315  21.050  -6.271  0.00  0.00           H
ATOM   1706 1HG  GLU  11      20.944  19.574  -3.662  0.00  0.00           H
ATOM   1707 2HG  GLU  11      21.853  18.865  -4.988  0.00  0.00           H
ATOM   1708  HE2 GLU  11      23.835  20.878  -2.329  0.00  0.00           H
ATOM   1709  N   HIS  12      19.646  23.728  -6.299  0.00  0.00           N
ATOM   1710  CA  HIS  12      19.691  25.027  -7.006  0.00  0.00           C
ATOM   1711  C   HIS  12      18.287  25.650  -7.211  0.00  0.00           C
ATOM   1712  O   HIS  12      17.746  25.705  -8.312  0.00  0.00           O
ATOM   1713  CB  HIS  12      20.675  24.904  -8.185  0.00  0.00           C
ATOM   1714  CG  HIS  12      20.560  23.817  -9.250  0.00  0.00           C
ATOM   1715  ND1 HIS  12      21.628  22.979  -9.519  0.00  0.00           N
ATOM   1716  CD2 HIS  12      19.362  23.138  -9.437  0.00  0.00           C
ATOM   1717  CE1 HIS  12      20.978  21.794  -9.708  0.00  0.00           C
ATOM   1718  NE2 HIS  12      19.607  21.805  -9.759  0.00  0.00           N
ATOM   1719  H   HIS  12      18.865  23.079  -6.376  0.00  0.00           H
ATOM   1720  HA  HIS  12      20.170  25.744  -6.361  0.00  0.00           H
```

FIG. 8 - 52

```
ATOM   1721  1HB  HIS    12      20.830  25.893  -8.648  0.00  0.00           H
ATOM   1722  2HB  HIS    12      21.556  24.631  -7.595  0.00  0.00           H
ATOM   1723  HD1  HIS    12      22.610  23.123  -9.240  0.00  0.00           H
ATOM   1724  HD2  HIS    12      18.550  23.512  -8.820  0.00  0.00           H
ATOM   1725  HE1  HIS    12      21.501  20.859  -9.492  0.00  0.00           H
ATOM   1726  HE2  HIS    12      18.947  21.045  -9.975  1.00  0.00           H
ATOM   1727  N    SER    13      17.691  26.036  -6.081  0.00  0.00           N
ATOM   1728  CA   SER    13      16.249  26.349  -5.974  0.00  0.00           C
ATOM   1729  C    SER    13      15.708  27.608  -6.698  0.00  0.00           C
ATOM   1730  O    SER    13      14.712  27.558  -7.420  0.00  0.00           O
ATOM   1731  CB   SER    13      15.885  26.343  -4.468  0.00  0.00           C
ATOM   1732  OG   SER    13      14.471  26.433  -4.292  0.00  0.00           O
ATOM   1733  H    SER    13      18.082  25.458  -5.350  0.00  0.00           H
ATOM   1734  HA   SER    13      15.801  25.510  -6.492  0.00  0.00           H
ATOM   1735  1HB  SER    13      16.258  25.440  -3.949  0.00  0.00           H
ATOM   1736  2HB  SER    13      16.375  27.194  -3.951  0.00  0.00           H
ATOM   1737  HG   SER    13      14.303  27.039  -3.558  0.00  0.00           H
ATOM   1738  N    ASN    14      16.489  28.672  -6.585  0.00  0.00           N
ATOM   1739  CA   ASN    14      16.473  29.812  -7.558  0.00  0.00           C
ATOM   1740  C    ASN    14      16.517  29.426  -9.077  0.00  0.00           C
ATOM   1741  O    ASN    14      15.874  30.064  -9.909  0.00  0.00           O
ATOM   1742  CB   ASN    14      17.637  30.802  -7.261  0.00  0.00           C
ATOM   1743  CG   ASN    14      17.717  31.430  -5.868  0.00  0.00           C
ATOM   1744  OD1  ASN    14      16.728  31.695  -5.199  0.00  0.00           O
ATOM   1745  ND2  ASN    14      18.906  31.704  -5.400  0.00  0.00           N
ATOM   1746  H    ASN    14      17.304  28.297  -6.096  0.00  0.00           H
ATOM   1747  HA   ASN    14      15.519  30.344  -7.424  0.00  0.00           H
ATOM   1748  1HB  ASN    14      18.599  30.315  -7.508  0.00  0.00           H
ATOM   1749  2HB  ASN    14      17.565  31.654  -7.964  0.00  0.00           H
ATOM   1750  1HD2 ASN    14      18.877  32.254  -4.535  0.00  0.00           H
ATOM   1751  2HD2 ASN    14      19.690  31.583  -6.045  0.00  0.00           H
ATOM   1752  N    LEU    15      17.281  28.377  -9.419  0.00  0.00           N
ATOM   1753  CA   LEU    15      17.453  27.899 -10.811  0.00  0.00           C
ATOM   1754  C    LEU    15      16.429  26.809 -11.303  0.00  0.00           C
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FIG. 8 - 53

```
ATOM   1755  O   LEU    15      16.447  26.440 -12.479  0.00  0.00           O
ATOM   1756  CB  LEU    15      18.956  27.495 -10.905  0.00  0.00           C
ATOM   1757  CG  LEU    15      19.958  28.657 -10.599  0.00  0.00           C
ATOM   1758  CD1 LEU    15      20.620  28.628  -9.208  0.00  0.00           C
ATOM   1759  CD2 LEU    15      21.040  28.757 -11.669  0.00  0.00           C
ATOM   1760  H   LEU    15      17.716  27.853  -8.649  0.00  0.00           H
ATOM   1761  HA  LEU    15      17.308  28.751 -11.496  0.00  0.00           H
ATOM   1762 1HB  LEU    15      19.167  26.614 -10.275  0.00  0.00           H
ATOM   1763 2HB  LEU    15      19.115  27.121 -11.936  0.00  0.00           H
ATOM   1764  HG  LEU    15      19.368  29.595 -10.613  0.00  0.00           H
ATOM   1765 1HD1 LEU    15      19.900  28.429  -8.394  0.00  0.00           H
ATOM   1766 2HD1 LEU    15      21.443  27.898  -9.135  0.00  0.00           H
ATOM   1767 3HD1 LEU    15      21.074  29.613  -8.978  0.00  0.00           H
ATOM   1768 1HD2 LEU    15      20.590  28.889 -12.670  0.00  0.00           H
ATOM   1769 2HD2 LEU    15      21.697  29.628 -11.493  0.00  0.00           H
ATOM   1770 3HD2 LEU    15      21.670  27.849 -11.697  0.00  0.00           H
ATOM   1771  N   CYS    16      15.545  26.290 -10.427  0.00  0.00           N
ATOM   1772  CA  CYS    16      14.463  25.336 -10.785  0.00  0.00           C
ATOM   1773  C   CYS    16      13.027  25.602 -10.206  0.00  0.00           C
ATOM   1774  O   CYS    16      12.068  24.944 -10.603  0.00  0.00           O
ATOM   1775  CB  CYS    16      15.012  23.961 -10.369  0.00  0.00           C
ATOM   1776  SG  CYS    16      16.243  23.486 -11.612  0.00  0.00           S
ATOM   1777  H   CYS    16      15.787  26.528  -9.458  0.00  0.00           H
ATOM   1778  HA  CYS    16      14.308  25.329 -11.884  0.00  0.00           H
ATOM   1779 1HB  CYS    16      15.396  23.966  -9.326  0.00  0.00           H
ATOM   1780 2HB  CYS    16      14.203  23.225 -10.383  0.00  0.00           H
TER    1781      CYS    16
HETATM 1782  N   NH2    17H     12.765  26.462  -9.243  0.00  0.00           N
HETATM 1783 1HN  NH2    17H     11.781  26.742  -9.205  0.00  0.00           H
HETATM 1784 2HN  NH2    17H     13.561  27.023  -8.899  0.00  0.00           H
ENDMDL
MODEL        9
ATOM   1785  N   GLY     1      14.562  17.015 -16.324  0.00  0.00           N
ATOM   1786  CA  GLY     1      15.859  17.600 -15.842  0.00  0.00           C
```

FIG. 8 - 54

```
ATOM   1787  C   GLY   1      16.143  17.408 -14.324  0.00  0.00           C
ATOM   1788  O   GLY   1      15.460  16.619 -13.674  0.00  0.00           O
ATOM   1789  1H  GLY   1      13.778  17.454 -15.820  1.00  0.00           H
ATOM   1790  2H  GLY   1      14.460  17.190 -17.334  1.00  0.00           H
ATOM   1791  3H  GLY   1      14.557  16.000 -16.150  1.00  0.00           H
ATOM   1792  1HA GLY   1      16.706  17.160 -16.407  0.00  0.00           H
ATOM   1793  2HA GLY   1      15.885  18.685 -16.071  0.00  0.00           H
ATOM   1794  N   CYS   2      17.111  18.125 -13.724  0.00  0.00           N
ATOM   1795  CA  CYS   2      17.437  17.922 -12.275  0.00  0.00           C
ATOM   1796  C   CYS   2      16.471  18.711 -11.299  0.00  0.00           C
ATOM   1797  O   CYS   2      16.000  18.158 -10.307  0.00  0.00           O
ATOM   1798  CB  CYS   2      18.911  18.333 -12.112  0.00  0.00           C
ATOM   1799  SG  CYS   2      19.241  18.754 -10.390  0.00  0.00           S
ATOM   1800  H   CYS   2      17.863  18.469 -14.331  0.00  0.00           H
ATOM   1801  HA  CYS   2      17.364  16.850 -11.999  0.00  0.00           H
ATOM   1802  1HB CYS   2      19.599  17.573 -12.519  0.00  0.00           H
ATOM   1803  2HB CYS   2      19.096  19.273 -12.669  0.00  0.00           H
ATOM   1804  N   CYS   3      16.127  19.980 -11.588  0.00  0.00           N
ATOM   1805  CA  CYS   3      14.826  20.600 -11.235  0.00  0.00           C
ATOM   1806  C   CYS   3      13.487  19.762 -11.375  0.00  0.00           C
ATOM   1807  O   CYS   3      12.507  20.103 -10.714  0.00  0.00           O
ATOM   1808  CB  CYS   3      14.880  21.721 -12.293  0.00  0.00           C
ATOM   1809  SG  CYS   3      16.179  22.947 -11.997  0.00  0.00           S
ATOM   1810  H   CYS   3      16.530  20.353 -12.450  0.00  0.00           H
ATOM   1811  HA  CYS   3      14.839  21.061 -10.203  0.00  0.00           H
ATOM   1812  1HB CYS   3      14.936  21.357 -13.339  0.00  0.00           H
ATOM   1813  2HB CYS   3      13.940  22.263 -12.269  0.00  0.00           H
ATOM   1814  N   SER   4      13.420  18.686 -12.185  0.00  0.00           N
ATOM   1815  CA  SER   4      12.322  17.678 -12.114  0.00  0.00           C
ATOM   1816  C   SER   4      12.332  16.659 -10.912  0.00  0.00           C
ATOM   1817  O   SER   4      11.322  16.001 -10.662  0.00  0.00           O
ATOM   1818  CB  SER   4      12.262  16.958 -13.467  0.00  0.00           C
ATOM   1819  OG  SER   4      12.267  17.813 -14.620  0.00  0.00           O
ATOM   1820  H   SER   4      14.301  18.380 -12.596  0.00  0.00           H
```

FIG. 8 - 55

```
ATOM   1821  HA  SER     4      11.365  18.182 -12.053  0.00  0.00           H
ATOM   1822 1HB  SER     4      13.091  16.258 -13.487  0.00  0.00           H
ATOM   1823 2HB  SER     4      11.370  16.320 -13.484  0.00  0.00           H
ATOM   1824  HG  SER     4      11.461  18.347 -14.562  0.00  0.00           H
ATOM   1825   N  ASN     5      13.423  16.565 -10.141  0.00  0.00           N
ATOM   1826  CA  ASN     5      13.518  15.810  -8.887  0.00  0.00           C
ATOM   1827   C  ASN     5      13.099  16.594  -7.592  0.00  0.00           C
ATOM   1828   O  ASN     5      13.054  17.828  -7.618  0.00  0.00           O
ATOM   1829  CB  ASN     5      15.006  15.397  -8.796  0.00  0.00           C
ATOM   1830  CG  ASN     5      15.453  14.037  -9.250  0.00  0.00           C
ATOM   1831 OD1  ASN     5      15.174  13.550 -10.336  0.00  0.00           O
ATOM   1832 ND2  ASN     5      16.300  13.461  -8.458  0.00  0.00           N
ATOM   1833   H  ASN     5      14.271  17.096 -10.359  0.00  0.00           H
ATOM   1834  HA  ASN     5      12.969  14.872  -8.977  0.00  0.00           H
ATOM   1835 1HB  ASN     5      15.578  15.875  -9.579  0.00  0.00           H
ATOM   1836 2IIB ASN     5      15.518  15.883  -7.969  0.00  0.00           H
ATOM   1837 1HD2 ASN     5      16.865  12.822  -9.013  0.00  0.00           H
ATOM   1838 2HD2 ASN     5      16.570  14.001  -7.632  0.00  0.00           H
ATOM   1839   N  PRO     6      12.920  15.946  -6.408  0.00  0.00           N
ATOM   1840  CA  PRO     6      12.932  16.658  -5.095  0.00  0.00           C
ATOM   1841   C  PRO     6      14.249  17.411  -4.715  0.00  0.00           C
ATOM   1842   O  PRO     6      14.277  18.623  -4.508  0.00  0.00           O
ATOM   1843  CB  PRO     6      12.519  15.524  -4.145  0.00  0.00           C
ATOM   1844  CG  PRO     6      13.109  14.267  -4.793  0.00  0.00           C
ATOM   1845  CD  PRO     6      12.800  14.476  -6.275  0.00  0.00           C
ATOM   1846  HA  PRO     6      12.147  17.406  -5.037  0.00  0.00           H
ATOM   1847 1HB  PRO     6      12.851  15.717  -3.113  0.00  0.00           H
ATOM   1848 2HB  PRO     6      11.413  15.445  -4.094  0.00  0.00           H
ATOM   1849 1HG  PRO     6      14.194  14.179  -4.620  0.00  0.00           H
ATOM   1850 2HG  PRO     6      12.703  13.341  -4.384  0.00  0.00           H
ATOM   1851 1HD  PRO     6      13.463  13.896  -6.938  0.00  0.00           H
ATOM   1852 2HD  PRO     6      11.777  14.144  -6.526  0.00  0.00           H
ATOM   1853   N  VAL     7      15.344  16.665  -4.645  0.00  0.00           N
ATOM   1854  CA  VAL     7      16.539  17.031  -3.829  0.00  0.00           C
```

FIG. 8 - 56

```
ATOM   1855  C   VAL  7      17.586  17.841  -4.634  0.00  0.00      C
ATOM   1856  O   VAL  7      17.982  18.935  -4.218  0.00  0.00      O
ATOM   1857  CB  VAL  7      17.053  15.688  -3.188  0.00  0.00      C
ATOM   1858  CG1 VAL  7      18.468  15.753  -2.564  0.00  0.00      C
ATOM   1859  CG2 VAL  7      16.125  15.159  -2.065  0.00  0.00      C
ATOM   1860  H   VAL  7      15.090  15.693  -4.842  0.00  0.00      H
ATOM   1861  HA  VAL  7      16.248  17.751  -3.042  0.00  0.00      H
ATOM   1862  HB  VAL  7      17.072  14.926  -4.005  0.00  0.00      H
ATOM   1863  1HG1 VAL  7      18.533  16.500  -1.749  0.00  0.00      H
ATOM   1864  2HG1 VAL  7      18.779  14.781  -2.130  0.00  0.00      H
ATOM   1865  3HG1 VAL  7      19.247  16.014  -3.305  0.00  0.00      H
ATOM   1866  1HG2 VAL  7      15.088  15.000  -2.409  0.00  0.00      H
ATOM   1867  2HG2 VAL  7      16.466  14.183  -1.666  0.00  0.00      H
ATOM   1868  3HG2 VAL  7      16.071  15.852  -1.204  0.00  0.00      H
ATOM   1869  N   CYS  8      18.013  17.345  -5.806  0.00  0.00      N
ATOM   1870  CA  CYS  8      18.874  18.128  -6.728  0.00  0.00      C
ATOM   1871  C   CYS  8      18.308  19.418  -7.392  0.00  0.00      C
ATOM   1872  O   CYS  8      19.043  20.354  -7.731  0.00  0.00      O
ATOM   1873  CB  CYS  8      19.661  17.215  -7.691  0.00  0.00      C
ATOM   1874  SG  CYS  8      18.806  17.128  -9.277  0.00  0.00      S
ATOM   1875  H   CYS  8      17.529  16.484  -6.028  0.00  0.00      H
ATOM   1876  HA  CYS  8      19.543  18.563  -6.011  0.00  0.00      H
ATOM   1877  1HB CYS  8      20.672  17.625  -7.871  0.00  0.00      H
ATOM   1878  2HB CYS  8      19.821  16.197  -7.286  0.00  0.00      H
ATOM   1879  N   HIS  9      16.978  19.488  -7.453  0.00  0.00      N
ATOM   1880  CA  HIS  9      16.208  20.736  -7.602  0.00  0.00      C
ATOM   1881  C   HIS  9      16.562  21.788  -6.505  0.00  0.00      C
ATOM   1882  O   HIS  9      16.679  22.972  -6.799  0.00  0.00      O
ATOM   1883  CB  HIS  9      14.705  20.315  -7.638  0.00  0.00      C
ATOM   1884  CG  HIS  9      13.498  21.237  -7.347  0.00  0.00      C
ATOM   1885  ND1 HIS  9      12.448  21.322  -8.241  0.00  0.00      N
ATOM   1886  CD2 HIS  9      13.438  22.355  -6.512  0.00  0.00      C
ATOM   1887  CE1 HIS  9      11.905  22.544  -7.934  0.00  0.00      C
ATOM   1888  NE2 HIS  9      12.388  23.200  -6.842  0.00  0.00      N
```

FIG. 8 - 57

```
ATOM   1889  H   HIS   9      16.544  18.625  -7.139  0.00  0.00           H
ATOM   1890  HA  HIS   9      16.472  21.160  -8.548  0.00  0.00           H
ATOM   1891  1HB HIS   9      14.536  19.651  -8.499  0.00  0.00           H
ATOM   1892  2HB HIS   9      14.624  19.629  -6.769  0.00  0.00           H
ATOM   1893  HD1 HIS   9      12.279  20.746  -9.087  0.00  0.00           H
ATOM   1894  HD2 HIS   9      14.311  22.656  -5.992  0.00  0.00           H
ATOM   1895  HE1 HIS   9      11.435  23.142  -8.716  0.00  0.00           H
ATOM   1896  HE2 HIS   9      12.068  24.070  -6.392  1.00  0.00           H
ATOM   1897  N   LEU  10      16.601  21.348  -5.248  0.00  0.00           N
ATOM   1898  CA  LEU  10      16.649  22.250  -4.046  0.00  0.00           C
ATOM   1899  C   LEU  10      18.035  22.865  -3.693  0.00  0.00           C
ATOM   1900  O   LEU  10      18.161  24.071  -3.484  0.00  0.00           O
ATOM   1901  CB  LEU  10      15.921  21.586  -2.847  0.00  0.00           C
ATOM   1902  CG  LEU  10      14.374  21.492  -2.958  0.00  0.00           C
ATOM   1903  CD1 LEU  10      13.820  20.581  -1.857  0.00  0.00           C
ATOM   1904  CD2 LEU  10      13.678  22.862  -2.867  0.00  0.00           C
ATOM   1905  H   LEU  10      16.792  20.326  -5.278  0.00  0.00           H
ATOM   1906  HA  LEU  10      16.075  23.150  -4.292  0.00  0.00           H
ATOM   1907  1HB LEU  10      16.351  20.578  -2.684  0.00  0.00           H
ATOM   1908  2HB LEU  10      16.162  22.134  -1.913  0.00  0.00           H
ATOM   1909  HG  LEU  10      14.108  21.029  -3.927  0.00  0.00           H
ATOM   1910  1HD1 LEU  10      14.248  19.563  -1.916  0.00  0.00           H
ATOM   1911  2HD1 LEU  10      14.032  20.969  -0.842  0.00  0.00           H
ATOM   1912  3HD1 LEU  10      12.723  20.461  -1.940  0.00  0.00           H
ATOM   1913  1HD2 LEU  10      13.901  23.380  -1.915  0.00  0.00           H
ATOM   1914  2HD2 LEU  10      13.974  23.546  -3.680  0.00  0.00           H
ATOM   1915  3HD2 LEU  10      12.577  22.767  -2.930  0.00  0.00           H
ATOM   1916  N   GLU  11      19.097  22.074  -3.805  0.00  0.00           N
ATOM   1917  CA  GLU  11      20.422  22.493  -4.284  0.00  0.00           C
ATOM   1918  C   GLU  11      20.588  23.645  -5.323  0.00  0.00           C
ATOM   1919  O   GLU  11      21.575  24.379  -5.312  0.00  0.00           O
ATOM   1920  CB  GLU  11      20.985  21.146  -4.812  0.00  0.00           C
ATOM   1921  CG  GLU  11      22.132  20.545  -4.001  0.00  0.00           C
ATOM   1922  CD  GLU  11      23.464  21.293  -4.099  0.00  0.00           C
```

FIG. 8 - 58

```
ATOM   1923  OE1 GLU  11      23.989  21.571  -5.174  0.00  0.00      O
ATOM   1924  OE2 GLU  11      23.985  21.606  -2.880  0.00  0.00      O
ATOM   1925  H   GLU  11      18.982  21.086  -3.534  1.00  0.00      H
ATOM   1926  HA  GLU  11      20.989  22.752  -3.406  0.00  0.00      H
ATOM   1927  1HB GLU  11      20.244  20.358  -4.817  0.00  0.00      H
ATOM   1928  2HB GLU  11      21.171  21.189  -5.873  0.00  0.00      H
ATOM   1929  1HG GLU  11      21.703  20.512  -2.987  0.00  0.00      H
ATOM   1930  2HG GLU  11      22.312  19.494  -4.291  0.00  0.00      H
ATOM   1931  HE2 GLU  11      24.818  22.073  -2.949  0.00  0.00      H
ATOM   1932  N   HIS  12      19.642  23.740  -6.267  0.00  0.00      N
ATOM   1933  CA  HIS  12      19.603  24.832  -7.272  0.00  0.00      C
ATOM   1934  C   HIS  12      18.182  25.479  -7.383  0.00  0.00      C
ATOM   1935  O   HIS  12      17.603  25.552  -8.465  0.00  0.00      O
ATOM   1936  CB  HIS  12      20.114  24.245  -8.617  0.00  0.00      C
ATOM   1937  CG  HIS  12      21.494  23.567  -8.642  0.00  0.00      C
ATOM   1938  ND1 HIS  12      21.606  22.191  -8.514  0.00  0.00      N
ATOM   1939  CD2 HIS  12      22.730  24.180  -8.342  0.00  0.00      C
ATOM   1940  CE1 HIS  12      22.890  22.081  -8.041  0.00  0.00      C
ATOM   1941  NE2 HIS  12      23.663  23.211  -7.976  0.00  0.00      N
ATOM   1942  H   HIS  12      18.841  23.129  -6.066  0.00  0.00      H
ATOM   1943  HA  HIS  12      20.266  25.652  -6.968  0.00  0.00      H
ATOM   1944  1HB HIS  12      19.349  23.509  -8.918  0.00  0.00      H
ATOM   1945  2HB HIS  12      20.071  25.045  -9.379  0.00  0.00      H
ATOM   1946  HD1 HIS  12      20.829  21.530  -8.372  0.00  0.00      H
ATOM   1947  HD2 HIS  12      22.856  25.248  -8.191  0.00  0.00      H
ATOM   1948  HE1 HIS  12      23.193  21.175  -7.510  0.00  0.00      H
ATOM   1949  HE2 HIS  12      24.657  23.315  -7.727  1.00  0.00      H
ATOM   1950  N   SER  13      17.592  25.911  -6.257  0.00  0.00      N
ATOM   1951  CA  SER  13      16.129  26.183  -6.159  0.00  0.00      C
ATOM   1952  C   SER  13      15.555  27.406  -6.926  0.00  0.00      C
ATOM   1953  O   SER  13      14.523  27.328  -7.592  0.00  0.00      O
ATOM   1954  CB  SER  13      15.676  26.175  -4.680  0.00  0.00      C
ATOM   1955  OG  SER  13      14.266  25.960  -4.598  0.00  0.00      O
ATOM   1956  H   SER  13      18.030  25.452  -5.473  0.00  0.00      H
```

FIG. 8 - 59

```
ATOM   1957  HA  SER  13      15.700  25.314  -6.640  0.00  0.00      H
ATOM   1958 1HB  SER  13      16.186  25.394  -4.091  0.00  0.00      H
ATOM   1959 2HB  SER  13      15.949  27.130  -4.185  0.00  0.00      H
ATOM   1960  HG  SER  13      13.942  26.453  -3.832  0.00  0.00      H
ATOM   1961   N  ASN  14      16.334  28.477  -6.887  0.00  0.00      N
ATOM   1962  CA  ASN  14      16.254  29.595  -7.870  0.00  0.00      C
ATOM   1963   C  ASN  14      16.476  29.228  -9.382  0.00  0.00      C
ATOM   1964   O  ASN  14      15.951  29.930 -10.245  0.00  0.00      O
ATOM   1965  CB  ASN  14      17.219  30.706  -7.366  0.00  0.00      C
ATOM   1966  CG  ASN  14      16.919  32.108  -7.895  0.00  0.00      C
ATOM   1967 OD1  ASN  14      16.133  32.850  -7.325  0.00  0.00      O
ATOM   1968 ND2  ASN  14      17.517  32.530  -8.979  0.00  0.00      N
ATOM   1969   H  ASN  14      17.186  28.126  -6.444  0.00  0.00      H
ATOM   1970  HA  ASN  14      15.222  29.984  -7.820  0.00  0.00      H
ATOM   1971 1HB  ASN  14      17.154  30.804  -6.265  0.00  0.00      H
ATOM   1972 2HB  ASN  14      18.273  30.439  -7.561  0.00  0.00      H
ATOM   1973 1HD2 ASN  14      17.172  33.448  -9.274  0.00  0.00      H
ATOM   1974 2HD2 ASN  14      17.957  31.818  -9.566  0.00  0.00      H
ATOM   1975   N  LEU  15      17.204  28.141  -9.718  0.00  0.00      N
ATOM   1976  CA  LEU  15      17.171  27.571 -11.102  0.00  0.00      C
ATOM   1977   C  LEU  15      16.031  26.521 -11.412  0.00  0.00      C
ATOM   1978   O  LEU  15      15.972  25.971 -12.515  0.00  0.00      O
ATOM   1979  CB  LEU  15      18.585  27.019 -11.451  0.00  0.00      C
ATOM   1980  CG  LEU  15      19.802  27.979 -11.329  0.00  0.00      C
ATOM   1981 CD1  LEU  15      21.109  27.217 -11.592  0.00  0.00      C
ATOM   1982 CD2  LEU  15      19.709  29.172 -12.296  0.00  0.00      C
ATOM   1983   H  LEU  15      17.459  27.540  -8.918  0.00  0.00      H
ATOM   1984  HA  LEU  15      16.970  28.389 -11.803  0.00  0.00      H
ATOM   1985 1HB  LEU  15      18.760  26.122 -10.834  0.00  0.00      H
ATOM   1986 2HB  LEU  15      18.558  26.636 -12.491  0.00  0.00      H
ATOM   1987  HG  LEU  15      19.848  28.381 -10.297  0.00  0.00      H
ATOM   1988 1HD1 LEU  15      21.252  26.381 -10.887  0.00  0.00      H
ATOM   1989 2HD1 LEU  15      21.143  26.801 -12.616  0.00  0.00      H
ATOM   1990 3HD1 LEU  15      21.989  27.881 -11.483  0.00  0.00      H
```

FIG. 8 - 60

```
ATOM   1991 1HD2 LEU    15      19.640  28.855 -13.353  0.00  0.00           H
ATOM   1992 2HD2 LEU    15      18.824  29.802 -12.088  0.00  0.00           H
ATOM   1993 3HD2 LEU    15      20.587  29.841 -12.214  0.00  0.00           H
ATOM   1994  N   CYS    16      15.146  26.209 -10.448  0.00  0.00           N
ATOM   1995  CA  CYS    16      14.210  25.087 -10.488  0.00  0.00           C
ATOM   1996  C   CYS    16      12.707  25.378 -10.166  0.00  0.00           C
ATOM   1997  O   CYS    16      11.817  24.719 -10.691  0.00  0.00           O
ATOM   1998  CB  CYS    16      14.875  24.209  -9.443  0.00  0.00           C
ATOM   1999  SG  CYS    16      16.333  23.318 -10.035  0.00  0.00           S
ATOM   2000  H   CYS    16      15.548  26.241  -9.507  0.00  0.00           H
ATOM   2001  HA  CYS    16      14.267  24.522 -11.403  0.00  0.00           H
ATOM   2002 1HB  CYS    16      15.050  24.770  -8.551  0.00  0.00           H
ATOM   2003 2HB  CYS    16      14.187  23.538  -9.012  0.00  0.00           H
TER    2004      CYS    16
HETATM 2005  N   NH2    17H     12.344  26.224  -9.219  0.00  0.00           N
HETATM 2006 1HN  NH2    17H     11.364  26.516  -9.291  0.00  0.00           H
HETATM 2007 2HN  NH2    17H     13.117  26.763  -8.793  0.00  0.00           H
ENDMDL
MODEL       10
ATOM   2008  N   GLY     1      14.432  13.271 -13.202  0.00  0.00           N
ATOM   2009  CA  GLY     1      15.517  14.193 -12.746  0.00  0.00           C
ATOM   2010  C   GLY     1      16.063  15.239 -13.751  0.00  0.00           C
ATOM   2011  O   GLY     1      15.808  15.141 -14.945  0.00  0.00           O
ATOM   2012 1H   GLY     1      13.609  13.821 -13.484  1.00  0.00           H
ATOM   2013 2H   GLY     1      14.766  12.717 -14.004  1.00  0.00           H
ATOM   2014 3H   GLY     1      14.174  12.637 -12.433  1.00  0.00           H
ATOM   2015 1HA  GLY     1      15.167  14.765 -11.870  0.00  0.00           H
ATOM   2016 2HA  GLY     1      16.397  13.615 -12.405  0.00  0.00           H
ATOM   2017  N   CYS     2      16.864  16.247 -13.386  0.00  0.00           N
ATOM   2018  CA  CYS     2      17.331  16.492 -11.994  0.00  0.00           C
ATOM   2019  C   CYS     2      16.351  17.440 -11.195  0.00  0.00           C
ATOM   2020  O   CYS     2      15.954  17.099 -10.087  0.00  0.00           O
ATOM   2021  CB  CYS     2      18.754  17.067 -12.108  0.00  0.00           C
ATOM   2022  SG  CYS     2      19.146  17.973 -10.596  0.00  0.00           S
```

FIG. 8 - 61

```
ATOM   2023  H   CYS   2      17.482  16.490 -14.163  0.00  0.00           H
ATOM   2024  HA  CYS   2      17.423  15.555 -11.414  0.00  0.00           H
ATOM   2025  1HB CYS   2      19.488  16.286 -12.371  0.00  0.00           H
ATOM   2026  2HB CYS   2      18.802  17.823 -12.917  0.00  0.00           H
ATOM   2027  N   CYS   3      15.940  18.608 -11.714  0.00  0.00           N
ATOM   2028  CA  CYS   3      14.788  19.392 -11.211  0.00  0.00           C
ATOM   2029  C   CYS   3      13.371  18.710 -11.150  0.00  0.00           C
ATOM   2030  O   CYS   3      12.558  19.085 -10.304  0.00  0.00           O
ATOM   2031  CB  CYS   3      14.913  20.601 -12.145  0.00  0.00           C
ATOM   2032  SG  CYS   3      16.186  21.689 -11.467  0.00  0.00           S
ATOM   2033  H   CYS   3      16.269  18.871 -12.647  0.00  0.00           H
ATOM   2034  HA  CYS   3      14.975  19.778 -10.184  0.00  0.00           H
ATOM   2035  1HB CYS   3      15.096  20.369 -13.215  0.00  0.00           H
ATOM   2036  2HB CYS   3      13.973  21.134 -12.169  0.00  0.00           H
ATOM   2037  N   SER   4      13.097  17.671 -11.957  0.00  0.00           N
ATOM   2038  CA  SER   4      12.028  16.680 -11.702  0.00  0.00           C
ATOM   2039  C   SER   4      12.317  15.546 -10.640  0.00  0.00           C
ATOM   2040  O   SER   4      11.478  14.671 -10.433  0.00  0.00           O
ATOM   2041  CB  SER   4      11.704  16.154 -13.119  0.00  0.00           C
ATOM   2042  OG  SER   4      12.809  15.582 -13.833  0.00  0.00           O
ATOM   2043  H   SER   4      13.821  17.372 -12.604  0.00  0.00           H
ATOM   2044  HA  SER   4      11.119  17.198 -11.331  0.00  0.00           H
ATOM   2045  1HB SER   4      10.925  15.399 -13.021  0.00  0.00           H
ATOM   2046  2HB SER   4      11.240  16.960 -13.726  0.00  0.00           H
ATOM   2047  HG  SER   4      12.656  15.783 -14.769  0.00  0.00           H
ATOM   2048  N   ASN   5      13.442  15.588  -9.904  0.00  0.00           N
ATOM   2049  CA  ASN   5      13.521  15.080  -8.516  0.00  0.00           C
ATOM   2050  C   ASN   5      13.137  16.199  -7.474  0.00  0.00           C
ATOM   2051  O   ASN   5      13.196  17.395  -7.788  0.00  0.00           O
ATOM   2052  CB  ASN   5      15.016  14.734  -8.245  0.00  0.00           C
ATOM   2053  CG  ASN   5      15.689  13.570  -8.946  0.00  0.00           C
ATOM   2054  OD1 ASN   5      15.290  13.040  -9.976  0.00  0.00           O
ATOM   2055  ND2 ASN   5      16.776  13.161  -8.352  0.00  0.00           N
ATOM   2056  H   ASN   5      14.126  16.304 -10.173  0.00  0.00           H
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FIG. 8 - 62

```
ATOM   2057  HA  ASN     5      12.847  14.208  -8.327  0.00  0.00           H
ATOM   2058 1HB  ASN     5      15.664  15.624  -8.324  0.00  0.00           H
ATOM   2059 2HB  ASN     5      15.103  14.503  -7.184  0.00  0.00           H
ATOM   2060 1HD2 ASN     5      16.997  12.194  -8.585  0.00  0.00           H
ATOM   2061 2HD2 ASN     5      16.926  13.620  -7.446  0.00  0.00           H
ATOM   2062  N   PRO     6      12.865  15.864  -6.187  0.00  0.00           N
ATOM   2063  CA  PRO     6      12.805  16.876  -5.088  0.00  0.00           C
ATOM   2064  C   PRO     6      14.139  17.612  -4.737  0.00  0.00           C
ATOM   2065  O   PRO     6      14.192  18.831  -4.583  0.00  0.00           O
ATOM   2066  CB  PRO     6      12.226  16.023  -3.941  0.00  0.00           C
ATOM   2067  CG  PRO     6      12.797  14.632  -4.222  0.00  0.00           C
ATOM   2068  CD  PRO     6      12.696  14.470  -5.727  0.00  0.00           C
ATOM   2069  HA  PRO     6      12.094  17.664  -5.336  0.00  0.00           H
ATOM   2070 1HB  PRO     6      12.483  16.408  -2.936  0.00  0.00           H
ATOM   2071 2HB  PRO     6      11.119  16.003  -3.992  0.00  0.00           H
ATOM   2072 1HG  PRO     6      13.849  14.562  -3.898  0.00  0.00           H
ATOM   2073 2HG  PRO     6      12.323  13.818  -3.692  0.00  0.00           H
ATOM   2074 1HD  PRO     6      13.461  13.753  -6.045  0.00  0.00           H
ATOM   2075 2HD  PRO     6      11.756  14.056  -6.132  0.00  0.00           H
ATOM   2076  N   VAL     7      15.217  16.844  -4.627  0.00  0.00           N
ATOM   2077  CA  VAL     7      16.438  17.235  -3.866  0.00  0.00           C
ATOM   2078  C   VAL     7      17.480  17.991  -4.722  0.00  0.00           C
ATOM   2079  O   VAL     7      17.900  19.088  -4.349  0.00  0.00           O
ATOM   2080  CB  VAL     7      16.958  15.921  -3.170  0.00  0.00           C
ATOM   2081 CG1 VAL     7      18.411  15.969  -2.634  0.00  0.00           C
ATOM   2082 CG2 VAL     7      16.089  15.512  -1.953  0.00  0.00           C
ATOM   2083  H   VAL     7      14.924  15.867  -4.742  0.00  0.00           H
ATOM   2084  HA  VAL     7      16.172  18.010  -3.120  0.00  0.00           H
ATOM   2085  HB  VAL     7      16.913  15.105  -3.937  0.00  0.00           H
ATOM   2086 1HG1 VAL     7      18.553  16.771  -1.883  0.00  0.00           H
ATOM   2087 2HG1 VAL     7      18.711  15.021  -2.147  0.00  0.00           H
ATOM   2088 3HG1 VAL     7      19.153  16.144  -3.434  0.00  0.00           H
ATOM   2089 1HG2 VAL     7      15.015  15.435  -2.193  0.00  0.00           H
ATOM   2090 2HG2 VAL     7      16.386  14.528  -1.538  0.00  0.00           H
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FIG. 8 - 63

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ATOM   2091 3HG2 VAL     7      16.165  16.240  -1.122  0.00  0.00           H
ATOM   2092  N   CYS     8      17.896  17.441  -5.872  0.00  0.00           N
ATOM   2093  CA  CYS     8      18.840  18.150  -6.784  0.00  0.00           C
ATOM   2094  C   CYS     8      18.348  19.404  -7.580  0.00  0.00           C
ATOM   2095  O   CYS     8      19.099  20.312  -7.945  0.00  0.00           O
ATOM   2096  CB  CYS     8      19.680  17.158  -7.605  0.00  0.00           C
ATOM   2097  SG  CYS     8      18.762  16.704  -9.078  0.00  0.00           S
ATOM   2098  H   CYS     8      17.375  16.592  -6.065  0.00  0.00           H
ATOM   2099  HA  CYS     8      19.470  18.622  -6.055  0.00  0.00           H
ATOM   2100 1HB  CYS     8      20.640  17.616  -7.911  0.00  0.00           H
ATOM   2101 2HB  CYS     8      19.952  16.254  -7.026  0.00  0.00           H
ATOM   2102  N   HIS     9      17.032  19.479  -7.703  0.00  0.00           N
ATOM   2103  CA  HIS     9      16.227  20.727  -7.819  0.00  0.00           C
ATOM   2104  C   HIS     9      16.624  21.855  -6.823  0.00  0.00           C
ATOM   2105  O   HIS     9      16.788  23.015  -7.177  0.00  0.00           O
ATOM   2106  CB  HIS     9      14.763  20.256  -7.651  0.00  0.00           C
ATOM   2107  CG  HIS     9      13.443  20.918  -7.294  0.00  0.00           C
ATOM   2108  ND1 HIS     9      12.247  20.457  -7.805  0.00  0.00           N
ATOM   2109  CD2 HIS     9      13.344  22.259  -7.060  0.00  0.00           C
ATOM   2110  CE1 HIS     9      11.538  21.628  -7.902  0.00  0.00           C
ATOM   2111  NE2 HIS     9      12.095  22.761  -7.389  0.00  0.00           N
ATOM   2112  H   HIS     9      16.613  18.615  -7.362  0.00  0.00           H
ATOM   2113  HA  HIS     9      16.271  21.075  -8.813  0.00  0.00           H
ATOM   2114 1HB  HIS     9      14.649  19.276  -7.962  0.00  0.00           H
ATOM   2115 2HB  HIS     9      14.896  19.917  -6.638  0.00  0.00           H
ATOM   2116  HD1 HIS     9      12.130  19.621  -8.402  0.00  0.00           H
ATOM   2117  HD2 HIS     9      14.281  22.747  -7.032  0.00  0.00           H
ATOM   2118  HE1 HIS     9      10.736  21.735  -8.629  0.00  0.00           H
ATOM   2119  HE2 HIS     9      11.703  23.707  -7.279  1.00  0.00           H
ATOM   2120  N   LEU    10      16.617  21.435  -5.568  0.00  0.00           N
ATOM   2121  CA  LEU    10      16.638  22.341  -4.368  0.00  0.00           C
ATOM   2122  C   LEU    10      18.027  22.739  -3.781  0.00  0.00           C
ATOM   2123  O   LEU    10      18.188  23.850  -3.278  0.00  0.00           O
ATOM   2124  CB  LEU    10      15.630  21.863  -3.289  0.00  0.00           C
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FIG. 8 - 64

```
ATOM   2125  CG  LEU  10      14.128  21.969  -3.659  0.00  0.00      C
ATOM   2126  CD1 LEU  10      13.257  21.341  -2.569  0.00  0.00      C
ATOM   2127  CD2 LEU  10      13.651  23.415  -3.911  0.00  0.00      C
ATOM   2128  H   LEU  10      16.593  20.389  -5.655  0.00  0.00      H
ATOM   2129  HA  LEU  10      16.278  23.327  -4.699  0.00  0.00      H
ATOM   2130  1HB LEU  10      15.876  20.820  -3.008  0.00  0.00      H
ATOM   2131  2HB LEU  10      15.790  22.441  -2.357  0.00  0.00      H
ATOM   2132  HG  LEU  10      13.954  21.370  -4.567  0.00  0.00      H
ATOM   2133  1HD1 LEU  10     13.528  20.283  -2.395  0.00  0.00      H
ATOM   2134  2HD1 LEU  10     13.350  21.873  -1.603  0.00  0.00      H
ATOM   2135  3HD1 LEU  10     12.187  21.348  -2.850  0.00  0.00      H
ATOM   2136  1HD2 LEU  10     13.817  24.068  -3.035  0.00  0.00      H
ATOM   2137  2HD2 LEU  10     14.162  23.892  -4.766  0.00  0.00      H
ATOM   2138  3HD2 LEU  10     12.570  23.456  -4.147  0.00  0.00      H
ATOM   2139  N   GLU  11      19.069  21.938  -4.007  0.00  0.00      N
ATOM   2140  CA  GLU  11      20.399  22.416  -4.408  0.00  0.00      C
ATOM   2141  C   GLU  11      20.555  23.700  -5.281  0.00  0.00      C
ATOM   2142  O   GLU  11      21.500  24.473  -5.140  0.00  0.00      O
ATOM   2143  CB  GLU  11      20.954  21.167  -5.114  0.00  0.00      C
ATOM   2144  CG  GLU  11      21.840  20.196  -4.329  0.00  0.00      C
ATOM   2145  CD  GLU  11      22.508  19.118  -5.190  0.00  0.00      C
ATOM   2146  OE1 GLU  11      22.471  19.103  -6.421  0.00  0.00      O
ATOM   2147  OE2 GLU  11      23.142  18.182  -4.430  0.00  0.00      O
ATOM   2148  H   GLU  11      18.933  20.923  -3.895  1.00  0.00      H
ATOM   2149  HA  GLU  11      20.982  22.550  -3.534  0.00  0.00      H
ATOM   2150  1HB GLU  11      20.163  20.573  -5.529  0.00  0.00      H
ATOM   2151  2HB GLU  11      21.427  21.465  -6.025  0.00  0.00      H
ATOM   2152  1HG GLU  11      22.603  20.766  -3.785  0.00  0.00      H
ATOM   2153  2HG GLU  11      21.193  19.725  -3.574  0.00  0.00      H
ATOM   2154  HE2 GLU  11      23.556  17.508  -4.970  0.00  0.00      H
ATOM   2155  N   HIS  12      19.653  23.856  -6.252  0.00  0.00      N
ATOM   2156  CA  HIS  12      19.614  24.970  -7.171  0.00  0.00      C
ATOM   2157  C   HIS  12      18.198  25.620  -7.181  0.00  0.00      C
ATOM   2158  O   HIS  12      17.517  25.648  -8.208  0.00  0.00      O
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FIG. 8 - 65

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ATOM   2159  CB  HIS  12      19.987  24.338  -8.497  0.00  0.00      C
ATOM   2160  CG  HIS  12      21.260  23.496  -8.717  0.00  0.00      C
ATOM   2161  ND1 HIS  12      21.235  22.113  -8.786  0.00  0.00      N
ATOM   2162  CD2 HIS  12      22.590  23.946  -8.584  0.00  0.00      C
ATOM   2163  CE1 HIS  12      22.567  21.817  -8.640  0.00  0.00      C
ATOM   2164  NE2 HIS  12      23.460  22.856  -8.554  0.00  0.00      N
ATOM   2165  H   HIS  12      18.949  23.151  -6.428  0.00  0.00      H
ATOM   2166  HA  HIS  12      20.338  25.733  -6.969  0.00  0.00      H
ATOM   2167  1HB HIS  12      19.070  23.909  -8.859  0.00  0.00      H
ATOM   2168  2HB HIS  12      20.015  25.190  -9.108  0.00  0.00      H
ATOM   2169  HD1 HIS  12      20.431  21.483  -8.629  0.00  0.00      H
ATOM   2170  HD2 HIS  12      22.868  24.979  -8.397  0.00  0.00      H
ATOM   2171  HE1 HIS  12      22.890  20.787  -8.465  0.00  0.00      H
ATOM   2172  HE2 HIS  12      24.487  22.836  -8.487  1.00  0.00      H
ATOM   2173  N   SER  13      17.704  26.045  -6.021  0.00  0.00      N
ATOM   2174  CA  SER  13      16.270  26.382  -5.845  0.00  0.00      C
ATOM   2175  C   SER  13      15.747  27.643  -6.596  0.00  0.00      C
ATOM   2176  O   SER  13      14.666  27.653  -7.178  0.00  0.00      O
ATOM   2177  CB  SER  13      15.918  26.402  -4.338  0.00  0.00      C
ATOM   2178  OG  SER  13      16.581  27.464  -3.647  0.00  0.00      O
ATOM   2179  H   SER  13      18.202  25.605  -5.263  0.00  0.00      H
ATOM   2180  HA  SER  13      15.806  25.516  -6.322  0.00  0.00      H
ATOM   2181  1HB SER  13      14.822  26.491  -4.195  0.00  0.00      H
ATOM   2182  2HB SER  13      16.190  25.446  -3.853  0.00  0.00      H
ATOM   2183  HG  SER  13      16.050  28.266  -3.728  0.00  0.00      H
ATOM   2184  N   ASN  14      16.631  28.630  -6.666  0.00  0.00      N
ATOM   2185  CA  ASN  14      16.617  29.686  -7.714  0.00  0.00      C
ATOM   2186  C   ASN  14      16.649  29.229  -9.214  0.00  0.00      C
ATOM   2187  O   ASN  14      16.140  29.970 -10.055  0.00  0.00      O
ATOM   2188  CB  ASN  14      17.764  30.675  -7.366  0.00  0.00      C
ATOM   2189  CG  ASN  14      17.580  32.098  -7.894  0.00  0.00      C
ATOM   2190  OD1 ASN  14      17.027  32.959  -7.226  0.00  0.00      O
ATOM   2191  ND2 ASN  14      18.027  32.409  -9.083  0.00  0.00      N
ATOM   2192  H   ASN  14      17.469  28.208  -6.256  0.00  0.00      H
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FIG. 8 - 66

```
ATOM   2193  HA  ASN  14      15.652  30.205  -7.612  0.00  0.00           H
ATOM   2194 1HB  ASN  14      17.858  30.795  -6.270  0.00  0.00           H
ATOM   2195 2HB  ASN  14      18.744  30.273  -7.686  0.00  0.00           H
ATOM   2196 1HD2 ASN  14      17.766  33.363  -9.347  0.00  0.00           H
ATOM   2197 2HD2 ASN  14      18.212  31.626  -9.713  0.00  0.00           H
ATOM   2198  N   LEU  15      17.196  28.048  -9.578  0.00  0.00           N
ATOM   2199  CA  LEU  15      16.978  27.488 -10.947  0.00  0.00           C
ATOM   2200  C   LEU  15      15.620  26.732 -11.192  0.00  0.00           C
ATOM   2201  O   LEU  15      15.232  26.553 -12.349  0.00  0.00           O
ATOM   2202  CB  LEU  15      18.203  26.629 -11.380  0.00  0.00           C
ATOM   2203  CG  LEU  15      19.612  27.283 -11.352  0.00  0.00           C
ATOM   2204  CD1 LEU  15      20.667  26.280 -11.838  0.00  0.00           C
ATOM   2205  CD2 LEU  15      19.705  28.551 -12.221  0.00  0.00           C
ATOM   2206  H   LEU  15      17.494  27.415  -8.810  0.00  0.00           H
ATOM   2207  HA  LEU  15      16.936  28.332 -11.647  0.00  0.00           H
ATOM   2208 1HB  LEU  15      18.214  25.707 -10.772  0.00  0.00           H
ATOM   2209 2HB  LEU  15      18.013  26.276 -12.414  0.00  0.00           H
ATOM   2210  HG  LEU  15      19.853  27.570 -10.309  0.00  0.00           H
ATOM   2211 1HD1 LEU  15      20.644  25.332 -11.275  0.00  0.00           H
ATOM   2212 2HD1 LEU  15      20.522  26.023 -12.905  0.00  0.00           H
ATOM   2213 3HD1 LEU  15      21.688  26.693 -11.743  0.00  0.00           H
ATOM   2214 1HD2 LEU  15      19.439  28.358 -13.278  0.00  0.00           H
ATOM   2215 2HD2 LEU  15      19.030  29.350 -11.862  0.00  0.00           H
ATOM   2216 3HD2 LEU  15      20.722  28.987 -12.218  0.00  0.00           H
ATOM   2217  N   CYS  16      14.934  26.226 -10.147  0.00  0.00           N
ATOM   2218  CA  CYS  16      13.785  25.290 -10.291  0.00  0.00           C
ATOM   2219  C   CYS  16      12.516  25.503  -9.392  0.00  0.00           C
ATOM   2220  O   CYS  16      11.554  24.743  -9.480  0.00  0.00           O
ATOM   2221  CB  CYS  16      14.428  23.909 -10.052  0.00  0.00           C
ATOM   2222  SG  CYS  16      15.528  23.569 -11.455  0.00  0.00           S
ATOM   2223  H   CYS  16      15.438  26.334  -9.266  0.00  0.00           H
ATOM   2224  HA  CYS  16      13.387  25.317 -11.325  0.00  0.00           H
ATOM   2225 1HB  CYS  16      14.926  23.857  -9.057  0.00  0.00           H
ATOM   2226 2HB  CYS  16      13.649  23.138 -10.044  0.00  0.00           H
```

FIG. 8 - 67

```
TER    2227      CYS    16
HETATM 2228  N   NH2  17H      12.419  26.431  -8.465  0.00  0.00          N
HETATM 2229  1HN NH2  17H      11.463  26.609  -8.143  0.00  0.00          H
HETATM 2230  2HN NH2  17H      13.230  27.059  -8.351  0.00  0.00          H
ENDMDL
MODEL       11
ATOM   2231  N   GLY    1      15.499  14.102 -12.760  0.00  0.00          N
ATOM   2232  CA  GLY    1      16.497  15.105 -12.271  0.00  0.00          C
ATOM   2233  C   GLY    1      17.120  16.049 -13.310  0.00  0.00          C
ATOM   2234  O   GLY    1      17.031  15.802 -14.506  0.00  0.00          O
ATOM   2235  1H  GLY    1      14.704  14.592 -13.195  1.00  0.00          H
ATOM   2236  2H  GLY    1      15.944  13.486 -13.455  1.00  0.00          H
ATOM   2237  3H  GLY    1      15.162  13.538 -11.967  1.00  0.00          H
ATOM   2238  1HA GLY    1      16.031  15.750 -11.507  0.00  0.00          H
ATOM   2239  2HA GLY    1      17.354  14.606 -11.782  0.00  0.00          H
ATOM   2240  N   CYS    2      17.811  17.143 -12.986  0.00  0.00          N
ATOM   2241  CA  CYS    2      18.003  17.720 -11.623  0.00  0.00          C
ATOM   2242  C   CYS    2      16.769  18.473 -11.013  0.00  0.00          C
ATOM   2243  O   CYS    2      16.168  17.953 -10.073  0.00  0.00          O
ATOM   2244  CB  CYS    2      19.326  18.507 -11.679  0.00  0.00          C
ATOM   2245  SG  CYS    2      20.134  18.683 -10.068  0.00  0.00          S
ATOM   2246  H   CYS    2      18.267  17.524 -13.813  0.00  0.00          H
ATOM   2247  HA  CYS    2      18.243  16.888 -10.939  0.00  0.00          H
ATOM   2248  1HB CYS    2      20.064  17.944 -12.278  0.00  0.00          H
ATOM   2249  2HB CYS    2      19.208  19.482 -12.187  0.00  0.00          H
ATOM   2250  N   CYS    3      16.336  19.613 -11.583  0.00  0.00          N
ATOM   2251  CA  CYS    3      15.010  20.268 -11.300  0.00  0.00          C
ATOM   2252  C   CYS    3      13.713  19.365 -11.245  0.00  0.00          C
ATOM   2253  O   CYS    3      12.814  19.640 -10.449  0.00  0.00          O
ATOM   2254  CB  CYS    3      14.930  21.346 -12.405  0.00  0.00          C
ATOM   2255  SG  CYS    3      13.464  22.388 -12.252  0.00  0.00          S
ATOM   2256  H   CYS    3      16.844  19.837 -12.445  0.00  0.00          H
ATOM   2257  HA  CYS    3      15.045  20.819 -10.321  0.00  0.00          H
ATOM   2258  1HB CYS    3      15.804  22.027 -12.382  0.00  0.00          H
```

FIG. 8 - 68

```
ATOM   2259 2HB CYS  3     14.913  20.901 -13.420  0.00  0.00           H
ATOM   2260  N  SER  4     13.643  18.272 -12.026  0.00  0.00           N
ATOM   2261  CA SER  4     12.575  17.241 -11.933  0.00  0.00           C
ATOM   2262  C  SER  4     12.717  16.123 -10.834  0.00  0.00           C
ATOM   2263  O  SER  4     11.845  15.261 -10.729  0.00  0.00           O
ATOM   2264  CB SER  4     12.459  16.673 -13.369  0.00  0.00           C
ATOM   2265  OG SER  4     13.652  16.046 -13.863  0.00  0.00           O
ATOM   2266  H  SER  4     14.490  18.046 -12.542  0.00  0.00           H
ATOM   2267  HA SER  4     11.608  17.735 -11.710  0.00  0.00           H
ATOM   2268 1HB SER  4     11.634  15.947 -13.393  0.00  0.00           H
ATOM   2269 2HB SER  4     12.141  17.476 -14.067  0.00  0.00           H
ATOM   2270  HG SER  4     13.568  16.053 -14.829  0.00  0.00           H
ATOM   2271  N  ASN  5     13.753  16.142  -9.976  0.00  0.00           N
ATOM   2272  CA ASN  5     13.712  15.477  -8.648  0.00  0.00           C
ATOM   2273  C  ASN  5     13.159  16.428  -7.516  0.00  0.00           C
ATOM   2274  O  ASN  5     13.225  17.653  -7.670  0.00  0.00           O
ATOM   2275  CB ASN  5     15.185  15.140  -8.295  0.00  0.00           C
ATOM   2276  CG ASN  5     15.843  13.954  -8.973  0.00  0.00           C
ATOM   2277  OD1 ASN  5     15.415  13.394  -9.974  0.00  0.00           O
ATOM   2278  ND2 ASN  5     16.937  13.541  -8.406  0.00  0.00           N
ATOM   2279  H  ASN  5     14.434  16.894 -10.132  0.00  0.00           H
ATOM   2280  HA ASN  5     13.105  14.549  -8.669  0.00  0.00           H
ATOM   2281 1HB ASN  5     15.834  16.032  -8.363  0.00  0.00           H
ATOM   2282 2HB ASN  5     15.211  14.889  -7.231  0.00  0.00           H
ATOM   2283 1HD2 ASN  5     17.101  12.554  -8.604  0.00  0.00           H
ATOM   2284 2HD2 ASN  5     17.118  14.008  -7.514  0.00  0.00           H
ATOM   2285  N  PRO  6     12.762  15.938  -6.307  0.00  0.00           N
ATOM   2286  CA PRO  6     12.725  16.787  -5.079  0.00  0.00           C
ATOM   2287  C  PRO  6     14.041  17.516  -4.651  0.00  0.00           C
ATOM   2288  O  PRO  6     14.085  18.734  -4.500  0.00  0.00           O
ATOM   2289  CB PRO  6     12.080  15.845  -4.057  0.00  0.00           C
ATOM   2290  CG PRO  6     12.367  14.420  -4.542  0.00  0.00           C
ATOM   2291  CD PRO  6     12.458  14.514  -6.047  0.00  0.00           C
ATOM   2292  HA PRO  6     12.022  17.599  -5.197  0.00  0.00           H
```

FIG. 8 - 69

```
ATOM   2293 1HB  PRO     6      12.422  16.065  -3.035  0.00  0.00           H
ATOM   2294 2HB  PRO     6      10.983  16.006  -4.040  0.00  0.00           H
ATOM   2295 1HG  PRO     6      13.320  14.028  -4.221  0.00  0.00           H
ATOM   2296 2HG  PRO     6      11.618  13.687  -4.194  0.00  0.00           H
ATOM   2297 1HD  PRO     6      13.176  13.802  -6.487  0.00  0.00           H
ATOM   2298 2HD  PRO     6      11.488  14.212  -6.414  0.00  0.00           H
ATOM   2299  N   VAL     7      15.123  16.766  -4.520  0.00  0.00           N
ATOM   2300  CA  VAL     7      16.361  17.176  -3.800  0.00  0.00           C
ATOM   2301  C   VAL     7      17.403  17.839  -4.733  0.00  0.00           C
ATOM   2302  O   VAL     7      17.901  18.932  -4.463  0.00  0.00           O
ATOM   2303  CB  VAL     7      16.877  15.851  -3.130  0.00  0.00           C
ATOM   2304  CG1 VAL     7      18.244  15.984  -2.437  0.00  0.00           C
ATOM   2305  CG2 VAL     7      15.926  15.247  -2.080  0.00  0.00           C
ATOM   2306  H   VAL     7      14.914  15.780  -4.630  0.00  0.00           H
ATOM   2307  HA  VAL     7      16.143  17.969  -3.059  0.00  0.00           H
ATOM   2308  HB  VAL     7      16.978  15.094  -3.939  0.00  0.00           H
ATOM   2309 1HG1 VAL     7      19.036  16.293  -3.142  0.00  0.00           H
ATOM   2310 2HG1 VAL     7      18.211  16.729  -1.621  0.00  0.00           H
ATOM   2311 3HG1 VAL     7      18.574  15.022  -1.999  0.00  0.00           H
ATOM   2312 1HG2 VAL     7      14.935  15.012  -2.509  0.00  0.00           H
ATOM   2313 2HG2 VAL     7      16.320  14.297  -1.675  0.00  0.00           H
ATOM   2314 3HG2 VAL     7      15.763  15.940  -1.236  0.00  0.00           H
ATOM   2315  N   CYS     8      17.720  17.182  -5.856  0.00  0.00           N
ATOM   2316  CA  CYS     8      18.599  17.767  -6.903  0.00 -0.00           C
ATOM   2317  C   CYS     8      18.168  19.114  -7.559  0.00  0.00           C
ATOM   2318  O   CYS     8      18.976  19.958  -7.940  0.00  0.00           O
ATOM   2319  CB  CYS     8      18.951  16.635  -7.903  0.00  0.00           C
ATOM   2320  SG  CYS     8      20.346  16.984  -9.013  0.00  0.00           S
ATOM   2321  H   CYS     8      17.357  16.233  -5.799  0.00  0.00           H
ATOM   2322  HA  CYS     8      19.428  18.095  -6.293  0.00  0.00           H
ATOM   2323 1HB  CYS     8      19.221  15.705  -7.364  0.00  0.00           H
ATOM   2324 2HB  CYS     8      18.075  16.381  -8.524  0.00  0.00           H
ATOM   2325  N   HIS     9      16.870  19.352  -7.546  0.00  0.00           N
ATOM   2326  CA  HIS     9      16.223  20.669  -7.713  0.00  0.00           C
```

FIG. 8 - 70

```
ATOM   2327  C   HIS   9      16.683  21.767  -6.697  0.00  0.00           C
ATOM   2328  O   HIS   9      16.869  22.928  -7.055  0.00  0.00           O
ATOM   2329  CB  HIS   9      14.712  20.290  -7.654  0.00  0.00           C
ATOM   2330  CG  HIS   9      13.514  21.175  -7.315  0.00  0.00           C
ATOM   2331  ND1 HIS   9      12.258  20.879  -7.804  0.00  0.00           N
ATOM   2332  CD2 HIS   9      13.498  22.443  -6.747  0.00  0.00           C
ATOM   2333  CE1 HIS   9      11.586  22.045  -7.538  0.00  0.00           C
ATOM   2334  NE2 HIS   9      12.240  23.026  -6.847  0.00  0.00           N
ATOM   2335  H   HIS   9      16.385  18.565  -7.123  0.00  0.00           H
ATOM   2336  HA  HIS   9      16.478  21.009  -8.700  0.00  0.00           H
ATOM   2337  1HB HIS   9      14.473  19.599  -8.475  0.00  0.00           H
ATOM   2338  2HB HIS   9      14.658  19.678  -6.730  0.00  0.00           H
ATOM   2339  HD1 HIS   9      12.013  20.122  -8.463  0.00  0.00           H
ATOM   2340  HD2 HIS   9      14.410  22.916  -6.457  0.00  0.00           H
ATOM   2341  HE1 HIS   9      10.669  22.285  -8.070  0.00  0.00           H
ATOM   2342  HE2 HIS   9      11.900  23.935  -6.501  1.00  0.00           H
ATOM   2343  N   LEU   10     16.765  21.369  -5.432  0.00  0.00           N
ATOM   2344  CA  LEU   10     16.835  22.294  -4.251  0.00  0.00           C
ATOM   2345  C   LEU   10     18.247  22.752  -3.769  0.00  0.00           C
ATOM   2346  O   LEU   10     18.412  23.870  -3.285  0.00  0.00           O
ATOM   2347  CB  LEU   10     15.971  21.736  -3.086  0.00  0.00           C
ATOM   2348  CG  LEU   10     14.437  21.708  -3.312  0.00  0.00           C
ATOM   2349  CD1 LEU   10     13.751  20.917  -2.192  0.00  0.00           C
ATOM   2350  CD2 LEU   10     13.800  23.108  -3.378  0.00  0.00           C
ATOM   2351  H   LEU   10     17.004  20.358  -5.442  0.00  0.00           H
ATOM   2352  HA  LEU   10     16.375  23.241  -4.558  0.00  0.00           H
ATOM   2353  1HB LEU   10     16.334  20.719  -2.836  0.00  0.00           H
ATOM   2354  2HB LEU   10     16.166  22.324  -2.166  0.00  0.00           H
ATOM   2355  HG  LEU   10     14.237  21.178  -4.262  0.00  0.00           H
ATOM   2356  1HD1 LEU   10     14.143  19.886  -2.120  0.00  0.00           H
ATOM   2357  2HD1 LEU   10     13.886  21.390  -1.201  0.00  0.00           H
ATOM   2358  3HD1 LEU   10     12.662  20.825  -2.367  0.00  0.00           H
ATOM   2359  1HD2 LEU   10     13.975  23.687  -2.451  0.00  0.00           H
ATOM   2360  2HD2 LEU   10     14.194  23.716  -4.209  0.00  0.00           H
```

FIG. 8 - 71

```
ATOM   2361 3HD2 LEU  10      12.705  23.056  -3.524  0.00  0.00           H
ATOM   2362  N   GLU  11      19.293  21.969  -4.048  0.00  0.00           N
ATOM   2363  CA  GLU  11      20.569  22.428  -4.615  0.00  0.00           C
ATOM   2364  C   GLU  11      20.706  23.839  -5.257  0.00  0.00           C
ATOM   2365  O   GLU  11      21.649  24.588  -5.018  0.00  0.00           O
ATOM   2366  CB  GLU  11      20.851  21.278  -5.640  0.00  0.00           C
ATOM   2367  CG  GLU  11      22.210  20.622  -5.488  0.00  0.00           C
ATOM   2368  CD  GLU  11      23.381  21.455  -6.010  0.00  0.00           C
ATOM   2369  OE1 GLU  11      23.430  21.855  -7.172  0.00  0.00           O
ATOM   2370  OE2 GLU  11      24.329  21.697  -5.065  0.00  0.00           O
ATOM   2371  H   GLU  11      19.197  20.963  -3.851  1.00  0.00           H
ATOM   2372  HA  GLU  11      21.292  22.346  -3.813  0.00  0.00           H
ATOM   2373 1HB  GLU  11      20.189  20.416  -5.526  0.00  0.00           H
ATOM   2374 2HB  GLU  11      20.641  21.586  -6.667  0.00  0.00           H
ATOM   2375 1HG  GLU  11      22.201  20.404  -4.410  0.00  0.00           H
ATOM   2376 2HG  GLU  11      22.236  19.643  -6.000  0.00  0.00           H
ATOM   2377  HE2 GLU  11      25.057  22.220  -5.398  0.00  0.00           H
ATOM   2378  N   HIS  12      19.750  24.127  -6.144  0.00  0.00           N
ATOM   2379  CA  HIS  12      19.674  25.376  -6.921  0.00  0.00           C
ATOM   2380  C   HIS  12      18.211  25.828  -7.155  0.00  0.00           C
ATOM   2381  O   HIS  12      17.701  25.791  -8.267  0.00  0.00           O
ATOM   2382  CB  HIS  12      20.679  25.261  -8.090  0.00  0.00           C
ATOM   2383  CG  HIS  12      20.646  24.114  -9.096  0.00  0.00           C
ATOM   2384  ND1 HIS  12      21.761  23.324  -9.317  0.00  0.00           N
ATOM   2385  CD2 HIS  12      19.490  23.369  -9.294  0.00  0.00           C
ATOM   2386  CE1 HIS  12      21.175  22.107  -9.507  0.00  0.00           C
ATOM   2387  NE2 HIS  12      19.807  22.049  -9.598  0.00  0.00           N
ATOM   2388  H   HIS  12      19.058  23.385  -6.204  0.00  0.00           H
ATOM   2389  HA  HIS  12      20.067  26.174  -6.319  0.00  0.00           H
ATOM   2390 1HB  HIS  12      20.781  26.228  -8.609  0.00  0.00           H
ATOM   2391 2HB  HIS  12      21.585  25.087  -7.498  0.00  0.00           H
ATOM   2392  HD1 HIS  12      22.705  23.477  -8.930  0.00  0.00           H
ATOM   2393  HD2 HIS  12      18.642  23.717  -8.714  0.00  0.00           H
ATOM   2394  HE1 HIS  12      21.732  21.209  -9.228  0.00  0.00           H
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FIG. 8 - 72

```
ATOM   2395  HE2 HIS  12      19.191  21.255  -9.825  1.00  0.00           H
ATOM   2396  N   SER  13      17.523  26.185  -6.068  0.00  0.00           N
ATOM   2397  CA  SER  13      16.046  26.357  -6.045  0.00  0.00           C
ATOM   2398  C   SER  13      15.403  27.496  -6.865  0.00  0.00           C
ATOM   2399  O   SER  13      14.404  27.297  -7.553  0.00  0.00           O
ATOM   2400  CB  SER  13      15.549  26.451  -4.576  0.00  0.00           C
ATOM   2401  OG  SER  13      16.041  25.406  -3.743  0.00  0.00           O
ATOM   2402  H   SER  13      17.917  25.664  -5.293  0.00  0.00           H
ATOM   2403  HA  SER  13      15.710  25.459  -6.555  0.00  0.00           H
ATOM   2404  1HB SER  13      15.848  27.426  -4.139  0.00  0.00           H
ATOM   2405  2HB SER  13      14.441  26.450  -4.540  0.00  0.00           H
ATOM   2406  HG  SER  13      16.085  25.742  -2.837  0.00  0.00           H
ATOM   2407  N   ASN  14      16.087  28.628  -6.837  0.00  0.00           N
ATOM   2408  CA  ASN  14      15.978  29.687  -7.890  0.00  0.00           C
ATOM   2409  C   ASN  14      16.141  29.192  -9.368  0.00  0.00           C
ATOM   2410  O   ASN  14      15.446  29.652 -10.272  0.00  0.00           O
ATOM   2411  CB  ASN  14      17.003  30.825  -7.614  0.00  0.00           C
ATOM   2412  CG  ASN  14      16.955  31.519  -6.250  0.00  0.00           C
ATOM   2413  OD1 ASN  14      15.923  31.659  -5.609  0.00  0.00           O
ATOM   2414  ND2 ASN  14      18.080  31.976  -5.766  0.00  0.00           N
ATOM   2415  H   ASN  14      16.935  28.369  -6.325  0.00  0.00           H
ATOM   2416  HA  ASN  14      14.964  30.108  -7.832  0.00  0.00           H
ATOM   2417  1HB ASN  14      18.025  30.447  -7.804  0.00  0.00           H
ATOM   2418  2HB ASN  14      16.854  31.625  -8.364  0.00  0.00           H
ATOM   2419  1HD2 ASN  14      17.952  32.539  -4.918  0.00  0.00           H
ATOM   2420  2HD2 ASN  14      18.893  31.941  -6.386  0.00  0.00           H
ATOM   2421  N   LEU  15      17.056  28.237  -9.587  0.00  0.00           N
ATOM   2422  CA  LEU  15      17.346  27.646 -10.917  0.00  0.00           C
ATOM   2423  C   LEU  15      16.491  26.380 -11.307  0.00  0.00           C
ATOM   2424  O   LEU  15      16.506  25.951 -12.460  0.00  0.00           O
ATOM   2425  CB  LEU  15      18.891  27.447 -10.955  0.00  0.00           C
ATOM   2426  CG  LEU  15      19.728  28.743 -10.689  0.00  0.00           C
ATOM   2427  CD1 LEU  15      20.301  28.891  -9.265  0.00  0.00           C
ATOM   2428  CD2 LEU  15      20.862  28.896 -11.699  0.00  0.00           C
```

FIG. 8 - 73

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ATOM   2429  H   LEU    15      17.521  27.858  -8.751  0.00  0.00           H
ATOM   2430  HA  LEU    15      17.106  28.398 -11.688  0.00  0.00           H
ATOM   2431 1HB  LEU    15      19.197  26.636 -10.274  0.00  0.00           H
ATOM   2432 2HB  LEU    15      19.127  27.049 -11.962  0.00  0.00           H
ATOM   2433  HG  LEU    15      19.035  29.599 -10.813  0.00  0.00           H
ATOM   2434 1HD1 LEU    15      19.566  28.646  -8.478  0.00  0.00           H
ATOM   2435 2HD1 LEU    15      21.206  28.285  -9.095  0.00  0.00           H
ATOM   2436 3HD1 LEU    15      20.605  29.941  -9.078  0.00  0.00           H
ATOM   2437 1HD2 LEU    15      20.469  28.910 -12.731  0.00  0.00           H
ATOM   2438 2HD2 LEU    15      21.407  29.846 -11.548  0.00  0.00           H
ATOM   2439 3HD2 LEU    15      21.589  28.067 -11.624  0.00  0.00           H
ATOM   2440  N   CYS    16      15.705  25.803 -10.377  0.00  0.00           N
ATOM   2441  CA  CYS    16      14.406  25.168 -10.709  0.00  0.00           C
ATOM   2442  C   CYS    16      13.208  26.159 -10.909  0.00  0.00           C
ATOM   2443  O   CYS    16      12.504  26.115 -11.910  0.00  0.00           O
ATOM   2444  CB  CYS    16      14.116  24.099  -9.660  0.00  0.00           C
ATOM   2445  SG  CYS    16      13.079  22.775 -10.326  0.00  0.00           S
ATOM   2446  H   CYS    16      15.878  26.220  -9.455  0.00  0.00           H
ATOM   2447  HA  CYS    16      14.494  24.599 -11.627  0.00  0.00           H
ATOM   2448 1HB  CYS    16      15.012  23.693  -9.163  0.00  0.00           H
ATOM   2449 2HB  CYS    16      13.559  24.594  -8.876  0.00  0.00           H
TER    2450      CYS    16
HETATM 2451  N   NH2    17H     12.890  27.026  -9.963  0.00  0.00           H
HETATM 2452 1HN  NH2    17H     12.218  27.733 -10.275  0.00  0.00           H
HETATM 2453 2HN  NH2    17H     13.533  27.077  -9.151  0.00  0.00           H
ENDMDL
MODEL        12
ATOM   2454  N   GLY     1      13.354  14.572 -15.326  0.00  0.00           N
ATOM   2455  CA  GLY     1      14.650  15.326 -15.254  0.00  0.00           C
ATOM   2456  C   GLY     1      15.107  15.718 -13.821  0.00  0.00           C
ATOM   2457  O   GLY     1      14.525  15.253 -12.844  0.00  0.00           O
ATOM   2458 1H  GLY     1      13.437  13.694 -14.794  1.00  0.00           H
ATOM   2459 2H  GLY     1      12.600  15.147 -14.924  1.00  0.00           H
ATOM   2460 3H  GLY     1      13.135  14.358 -16.309  1.00  0.00           H
```

FIG. 8 - 74

```
ATOM   2461 1HA  GLY     1      15.460  14.728 -15.718  0.00  0.00           H
ATOM   2462 2HA  GLY     1      14.578  16.248 -15.866  0.00  0.00           H
ATOM   2463  H   CYS     2      16.119  16.588 -13.668  0.00  0.00           N
ATOM   2464  CA  CYS     2      16.688  16.913 -12.319  0.00  0.00           C
ATOM   2465  C   CYS     2      15.766  17.849 -11.440  0.00  0.00           C
ATOM   2466  O   CYS     2      15.508  17.548 -10.277  0.00  0.00           O
ATOM   2467  CB  CYS     2      18.081  17.504 -12.618  0.00  0.00           C
ATOM   2468  SG  CYS     2      18.692  18.566 -11.292  0.00  0.00           S
ATOM   2469  H   CYS     2      16.711  16.753 -14.489  0.00  0.00           H
ATOM   2470  HA  CYS     2      16.838  15.983 -11.733  0.00  0.00           H
ATOM   2471 1HB  CYS     2      18.812  16.724 -12.897  0.00  0.00           H
ATOM   2472 2HB  CYS     2      18.010  18.197 -13.478  0.00  0.00           H
ATOM   2473  N   CYS     3      15.199  18.934 -11.999  0.00  0.00           N
ATOM   2474  CA  CYS     3      13.934  19.557 -11.543  0.00  0.00           C
ATOM   2475  C   CYS     3      12.694  18.648 -11.179  0.00  0.00           C
ATOM   2476  O   CYS     3      11.913  19.029 -10.304  0.00  0.00           O
ATOM   2477  CB  CYS     3      13.681  20.386 -12.822  0.00  0.00           C
ATOM   2478  SG  CYS     3      14.895  21.703 -13.054  0.00  0.00           S
ATOM   2479  H   CYS     3      15.438  19.131 -12.973  0.00  0.00           H
ATOM   2480  HA  CYS     3      14.106  20.251 -10.671  0.00  0.00           H
ATOM   2481 1HB  CYS     3      13.585  19.784 -13.748  0.00  0.00           H
ATOM   2482 2HB  CYS     3      12.718  20.874 -12.731  0.00  0.00           H
ATOM   2483  N   SER     4      12.517  17.469 -11.811  0.00  0.00           N
ATOM   2484  CA  SER     4      11.561  16.421 -11.349  0.00  0.00           C
ATOM   2485  C   SER     4      11.879  15.671 -10.001  0.00  0.00           C
ATOM   2486  O   SER     4      10.982  15.068  -9.412  0.00  0.00           O
ATOM   2487  CB  SER     4      11.352  15.420 -12.497  0.00  0.00           C
ATOM   2488  OG  SER     4      11.215  15.987 -13.809  0.00  0.00           O
ATOM   2489  H   SER     4      13.295  17.164 -12.394  0.00  0.00           H
ATOM   2490  HA  SER     4      10.580  16.864 -11.213  0.00  0.00           H
ATOM   2491 1HB  SER     4      12.183  14.721 -12.457  0.00  0.00           H
ATOM   2492 2HB  SER     4      10.471  14.809 -12.267  0.00  0.00           H
ATOM   2493  HG  SER     4      10.444  16.572 -13.773  0.00  0.00           H
ATOM   2494  N   ASN     5      13.116  15.749  -9.489  0.00  0.00           N
```

FIG. 8 - 75

```
ATOM   2495  CA  ASN     5      13.502  15.214  -8.170  0.00  0.00      C
ATOM   2496  C   ASN     5      13.265  16.250  -7.015  0.00  0.00      C
ATOM   2497  O   ASN     5      13.267  17.464  -7.256  0.00  0.00      O
ATOM   2498  CB  ASN     5      15.039  14.979  -8.240  0.00  0.00      C
ATOM   2499  CG  ASN     5      15.570  13.842  -9.092  0.00  0.00      C
ATOM   2500  OD1 ASN     5      15.547  13.842 -10.314  0.00  0.00      O
ATOM   2501  ND2 ASN     5      16.174  12.897  -8.432  0.00  0.00      N
ATOM   2502  H   ASN     5      13.833  16.147 -10.100  0.00  0.00      H
ATOM   2503  HA  ASN     5      12.962  14.274  -7.919  0.00  0.00      H
ATOM   2504  1HB ASN     5      15.569  15.900  -8.535  0.00  0.00      H
ATOM   2505  2HB ASN     5      15.409  14.806  -7.225  0.00  0.00      H
ATOM   2506 1HD2 ASN     5      16.707  12.280  -9.034  0.00  0.00      H
ATOM   2507 2HD2 ASN     5      16.358  13.135  -7.454  0.00  0.00      H
ATOM   2508  N   PRO     6      13.172  15.822  -5.727  0.00  0.00      N
ATOM   2509  CA  PRO     6      13.241  16.757  -4.567  0.00  0.00      C
ATOM   2510  C   PRO     6      14.606  17.500  -4.419  0.00  0.00      C
ATOM   2511  O   PRO     6      14.713  18.717  -4.530  0.00  0.00      O
ATOM   2512  CB  PRO     6      12.825  15.823  -3.410  0.00  0.00      C
ATOM   2513  CG  PRO     6      13.365  14.455  -3.838  0.00  0.00      C
ATOM   2514  CD  PRO     6      13.132  14.396  -5.337  0.00  0.00      C
ATOM   2515  HA  PRO     6      12.497  17.544  -4.667  0.00  0.00      H
ATOM   2516 1HB  PRO     6      13.205  16.154  -2.425  0.00  0.00      H
ATOM   2517 2HB  PRO     6      11.719  15.790  -3.321  0.00  0.00      H
ATOM   2518 1HG  PRO     6      14.439  14.365  -3.606  0.00  0.00      H
ATOM   2519 2HG  PRO     6      12.926  13.603  -3.336  0.00  0.00      H
ATOM   2520 1HD  PRO     6      13.907  13.762  -5.783  0.00  0.00      H
ATOM   2521 2HD  PRO     6      12.179  13.944  -5.663  0.00  0.00      H
ATOM   2522  N   VAL     7      15.657  16.709  -4.279  0.00  0.00      N
ATOM   2523  CA  VAL     7      17.050  17.147  -4.030  0.00  0.00      C
ATOM   2524  C   VAL     7      17.682  17.887  -5.228  0.00  0.00      C
ATOM   2525  O   VAL     7      18.138  19.025  -5.096  0.00  0.00      O
ATOM   2526  CB  VAL     7      17.789  15.814  -3.635  0.00  0.00      C
ATOM   2527  CG1 VAL     7      19.321  15.925  -3.548  0.00  0.00      C
ATOM   2528  CG2 VAL     7      17.336  15.221  -2.287  0.00  0.00      C
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FIG. 8 - 76

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ATOM   2529  H   VAL  7      15.398  15.726  -4.369  0.00  0.00      H
ATOM   2530  HA  VAL  7      17.061  17.912  -3.232  0.00  0.00      H
ATOM   2531  HB  VAL  7      17.558  15.055  -4.422  0.00  0.00      H
ATOM   2532  1HG1 VAL  7     19.627  16.676  -2.795  0.00  0.00     H
ATOM   2533  2HG1 VAL  7     19.782  14.959  -3.271  0.00  0.00     H
ATOM   2534  3HG1 VAL  7     19.764  16.217  -4.517  0.00  0.00     H
ATOM   2535  1HG2 VAL  7     16.249  15.031  -2.269  0.00  0.00     H
ATOM   2536  2HG2 VAL  7     17.828  14.251  -2.087  0.00  0.00     H
ATOM   2537  3HG2 VAL  7     17.564  15.904  -1.450  0.00  0.00     H
ATOM   2538  N   CYS  8      17.712  17.245  -6.401  0.00  0.00      N
ATOM   2539  CA  CYS  8      18.297  17.863  -7.622  0.00  0.00      C
ATOM   2540  C   CYS  8      17.652  19.136  -8.237  0.00  0.00      C
ATOM   2541  O   CYS  8      18.298  19.955  -8.894  0.00  0.00      O
ATOM   2542  CB  CYS  8      18.685  16.783  -8.651  0.00  0.00      C
ATOM   2543  SG  CYS  8      19.739  17.468  -9.962  0.00  0.00     S
ATOM   2544  H   CYS  8      17.410  16.284  -6.251  0.00  0.00      H
ATOM   2545  HA  CYS  8      19.166  18.324  -7.181  0.00  0.00      H
ATOM   2546  1HB CYS  8      19.243  15.955  -8.171  0.00  0.00      H
ATOM   2547  2HB CYS  8      17.791  16.330  -9.116  0.00  0.00      H
ATOM   2548  N   HIS  9      16.420  19.382  -7.848  0.00  0.00      N
ATOM   2549  CA  HIS  9      15.751  20.684  -7.982  0.00  0.00      C
ATOM   2550  C   HIS  9      16.288  21.736  -6.932  0.00  0.00      C
ATOM   2551  O   HIS  9      16.554  22.898  -7.243  0.00  0.00      O
ATOM   2552  CB  HIS  9      14.251  20.284  -7.886  0.00  0.00      C
ATOM   2553  CG  HIS  9      13.055  21.163  -7.546  0.00  0.00      C
ATOM   2554  ND1 HIS  9      11.791  20.822  -7.985  0.00  0.00     N
ATOM   2555  CD2 HIS  9      13.086  22.519  -7.255  0.00  0.00      C
ATOM   2556  CE1 HIS  9      11.162  22.041  -7.965  0.00  0.00      C
ATOM   2557  NE2 HIS  9      11.853  23.116  -7.481  0.00  0.00     N
ATOM   2558  H   HIS  9      16.024  18.603  -7.329  0.00  0.00      H
ATOM   2559  HA  HIS  9      15.955  21.034  -8.974  0.00  0.00      H
ATOM   2560  1HB HIS  9      14.005  19.522  -8.638  0.00  0.00      H
ATOM   2561  2HB HIS  9      14.256  19.741  -6.916  0.00  0.00      H
ATOM   2562  HD1 HIS  9      11.531  19.975  -8.518  0.00  0.00      H
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FIG. 8 - 77

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ATOM   2563  HD2 HIS     9      14.030  23.009  -7.124  0.00  0.00           H
ATOM   2564  HE1 HIS     9      10.220  22.192  -8.488  0.00  0.00           H
ATOM   2565  HE2 HIS     9      11.548  24.088  -7.328  1.00  0.00           H
ATOM   2566  N   LEU    10      16.311  21.289  -5.679  0.00  0.00           N
ATOM   2567  CA  LEU    10      16.377  22.144  -4.445  0.00  0.00           C
ATOM   2568  C   LEU    10      17.760  22.473  -3.820  0.00  0.00           C
ATOM   2569  O   LEU    10      17.890  23.482  -3.129  0.00  0.00           O
ATOM   2570  CB  LEU    10      15.351  21.636  -3.398  0.00  0.00           C
ATOM   2571  CG  LEU    10      13.864  21.683  -3.834  0.00  0.00           C
ATOM   2572  CD1 LEU    10      12.967  20.942  -2.840  0.00  0.00           C
ATOM   2573  CD2 LEU    10      13.324  23.116  -4.004  0.00  0.00           C
ATOM   2574  H   LEU    10      16.722  20.341  -5.756  0.00  0.00           H
ATOM   2575  HA  LEU    10      16.040  23.155  -4.728  0.00  0.00           H
ATOM   2576  1HB LEU    10      15.630  20.602  -3.117  0.00  0.00           H
ATOM   2577  2HB LEU    10      15.460  22.214  -2.460  0.00  0.00           H
ATOM   2578  HG  LEU    10      13.796  21.140  -4.797  0.00  0.00           H
ATOM   2579  1HD1 LEU   10      13.290  19.894  -2.705  0.00  0.00           H
ATOM   2580  2HD1 LEU   10      12.969  21.420  -1.843  0.00  0.00           H
ATOM   2581  3HD1 LEU   10      11.919  20.907  -3.191  0.00  0.00           H
ATOM   2582  1HD2 LEU   10      13.416  23.712  -3.076  0.00  0.00           H
ATOM   2583  2HD2 LEU   10      13.857  23.672  -4.790  0.00  0.00           H
ATOM   2584  3HD2 LEU   10      12.258  23.127  -4.297  0.00  0.00           H
ATOM   2585  N   GLU    11      18.818  21.722  -4.151  0.00  0.00           N
ATOM   2586  CA  GLU    11      20.192  22.246  -4.286  0.00  0.00           C
ATOM   2587  C   GLU    11      20.452  23.699  -4.747  0.00  0.00           C
ATOM   2588  O   GLU    11      21.407  24.357  -4.335  0.00  0.00           O
ATOM   2589  CB  GLU    11      20.855  21.223  -5.225  0.00  0.00           C
ATOM   2590  CG  GLU    11      20.374  21.058  -6.666  0.00  0.00           C
ATOM   2591  CD  GLU    11      21.342  20.441  -7.665  0.00  0.00           C
ATOM   2592  OE1 GLU    11      21.674  19.157  -7.352  0.00  0.00           O
ATOM   2593  OE2 GLU    11      21.773  21.058  -8.633  0.00  0.00           O
ATOM   2594  H   GLU    11      18.664  20.718  -4.321  1.00  0.00           H
ATOM   2595  HA  GLU    11      20.702  22.154  -3.341  0.00  0.00           H
ATOM   2596  1HB GLU    11      21.906  21.464  -5.251  0.00  0.00           H
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FIG. 8 - 78

```
ATOM   2597  2HB  GLU  11      20.744  20.261  -4.757  0.00  0.00      H
ATOM   2598  1HG  GLU  11      19.428  20.512  -6.677  0.00  0.00      H
ATOM   2599  2HG  GLU  11      20.124  22.058  -6.983  0.00  0.00      H
ATOM   2600  HE1  GLU  11      22.291  18.796  -7.989  0.00  0.00      H
ATOM   2601  N    HIS  12      19.626  24.107  -5.707  0.00  0.00      N
ATOM   2602  CA   HIS  12      19.818  25.374  -6.428  0.00  0.00      C
ATOM   2603  C    HIS  12      18.733  26.484  -6.333  0.00  0.00      C
ATOM   2604  O    HIS  12      19.042  27.663  -6.454  0.00  0.00      O
ATOM   2605  CB   HIS  12      20.277  24.968  -7.827  0.00  0.00      C
ATOM   2606  CG   HIS  12      21.792  24.962  -8.073  0.00  0.00      C
ATOM   2607  ND1  HIS  12      22.510  23.780  -8.091  0.00  0.00      N
ATOM   2608  CD2  HIS  12      22.679  26.050  -7.905  0.00  0.00      C
ATOM   2609  CE1  HIS  12      23.778  24.226  -7.847  0.00  0.00      C
ATOM   2610  NE2  HIS  12      23.986  25.580  -7.769  0.00  0.00      N
ATOM   2611  H    HIS  12      19.186  23.263  -6.127  0.00  0.00      H
ATOM   2612  HA   HIS  12      20.646  25.870  -6.000  0.00  0.00      H
ATOM   2613  1HB  HIS  12      19.871  24.005  -8.071  0.00  0.00      H
ATOM   2614  2HB  HIS  12      19.701  25.532  -8.524  0.00  0.00      H
ATOM   2615  HD1  HIS  12      22.195  22.809  -8.254  0.00  0.00      H
ATOM   2616  HD2  HIS  12      22.355  27.074  -7.739  0.00  0.00      H
ATOM   2617  HE1  HIS  12      24.554  23.506  -7.580  0.00  0.00      H
ATOM   2618  HE2  HIS  12      24.864  26.105  -7.645  1.00  0.00      H
ATOM   2619  N    SER  13      17.502  26.066  -6.092  0.00  0.00      N
ATOM   2620  CA   SER  13      16.275  26.291  -6.922  0.00  0.00      C
ATOM   2621  C    SER  13      16.016  27.519  -7.866  0.00  0.00      C
ATOM   2622  O    SER  13      14.946  27.637  -8.466  0.00  0.00      O
ATOM   2623  CB   SER  13      15.085  26.087  -5.953  0.00  0.00      C
ATOM   2624  OG   SER  13      13.888  25.783  -6.677  0.00  0.00      O
ATOM   2625  H    SER  13      17.824  25.106  -6.087  0.00  0.00      H
ATOM   2626  HA   SER  13      16.259  25.417  -7.601  0.00  0.00      H
ATOM   2627  1HB  SER  13      15.275  25.276  -5.225  0.00  0.00      H
ATOM   2628  2HB  SER  13      14.934  26.990  -5.326  0.00  0.00      H
ATOM   2629  HG   SER  13      13.655  26.591  -7.161  0.00  0.00      H
ATOM   2630  N    ASN  14      17.065  28.268  -8.166  0.00  0.00      N
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FIG. 8 - 79

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ATOM   2631  CA  ASN  14      17.267  28.960  -9.478  0.00  0.00           C
ATOM   2632  C   ASN  14      16.981  28.145 -10.777  0.00  0.00           C
ATOM   2633  O   ASN  14      16.450  28.632 -11.772  0.00  0.00           O
ATOM   2634  CB  ASN  14      18.711  29.560  -9.501  0.00  0.00           C
ATOM   2635  CG  ASN  14      19.898  28.649  -9.888  0.00  0.00           C
ATOM   2636  OD1 ASN  14      20.367  27.822  -9.118  0.00  0.00           O
ATOM   2637  ND2 ASN  14      20.329  28.664 -11.129  0.00  0.00           N
ATOM   2638  H   ASN  14      17.839  27.949  -7.552  0.00  0.00           H
ATOM   2639  HA  ASN  14      16.538  29.780  -9.510  0.00  0.00           H
ATOM   2640  1HB ASN  14      18.691  30.416 -10.194  0.00  0.00           H
ATOM   2641  2HB ASN  14      18.947  29.985  -8.512  0.00  0.00           H
ATOM   2642  1HD2 ASN  14      20.827  27.815 -11.424  0.00  0.00           H
ATOM   2643  2HD2 ASN  14      19.856  29.331 -11.747  0.00  0.00           H
ATOM   2644  N   LEU  15      17.434  26.894 -10.735  0.00  0.00           N
ATOM   2645  CA  LEU  15      17.465  25.958 -11.833  0.00  0.00           C
ATOM   2646  C   LEU  15      16.094  25.226 -12.112  0.00  0.00           C
ATOM   2647  O   LEU  15      15.892  24.667 -13.190  0.00  0.00           O
ATOM   2648  CB  LEU  15      18.645  25.153 -11.154  0.00  0.00           C
ATOM   2649  CG  LEU  15      19.027  23.885 -11.860  0.00  0.00           C
ATOM   2650  CD1 LEU  15      19.644  24.197 -13.232  0.00  0.00           C
ATOM   2651  CD2 LEU  15      19.959  22.970 -11.051  0.00  0.00           C
ATOM   2652  H   LEU  15      17.818  26.478  -9.879  0.00  0.00           H
ATOM   2653  HA  LEU  15      17.789  26.452 -12.767  0.00  0.00           H
ATOM   2654  1HB LEU  15      19.574  25.759 -11.047  0.00  0.00           H
ATOM   2655  2HB LEU  15      18.371  24.803 -10.132  0.00  0.00           H
ATOM   2656  HG  LEU  15      18.016  23.473 -11.871  0.00  0.00           H
ATOM   2657  1HD1 LEU  15      18.960  24.783 -13.875  0.00  0.00           H
ATOM   2658  2HD1 LEU  15      20.568  24.802 -13.127  0.00  0.00           H
ATOM   2659  3HD1 LEU  15      19.909  23.284 -13.788  0.00  0.00           H
ATOM   2660  1HD2 LEU  15      19.521  22.672 -10.081  0.00  0.00           H
ATOM   2661  2HD2 LEU  15      20.167  22.028 -11.593  0.00  0.00           H
ATOM   2662  3HD2 LEU  15      20.939  23.443 -10.850  0.00  0.00           H
ATOM   2663  N   CYS  16      15.198  25.175 -11.109  0.00  0.00           N
ATOM   2664  CA  CYS  16      13.936  24.408 -11.131  0.00  0.00           C
```

FIG. 8 - 80

```
ATOM   2665  C   CYS  16      12.679  25.064 -10.450  0.00  0.00           C
ATOM   2666  O   CYS  16      11.597  24.482 -10.447  0.00  0.00           O
ATOM   2667  CB  CYS  16      14.330  23.126 -10.385  0.00  0.00           C
ATOM   2668  SG  CYS  16      15.612  22.205 -11.261  0.00  0.00           S
ATOM   2669  H   CYS  16      15.573  25.599 -10.260  0.00  0.00           H
ATOM   2670  HA  CYS  16      13.634  24.165 -12.170  0.00  0.00           H
ATOM   2671 1HB  CYS  16      14.651  23.335  -9.351  0.00  0.00           H
ATOM   2672 2HB  CYS  16      13.446  22.487 -10.298  0.00  0.00           H
TER    2673      CYS  16
HETATM 2674  N   NH2  17H     12.720  26.210  -9.795  0.00  0.00           N
HETATM 2675 1HN  NH2  17H     11.793  26.617  -9.632  0.00  0.00           H
HETATM 2676 2HN  NH2  17H     13.621  26.710  -9.784  0.00  0.00           H
ENDMDL
MODEL       13
ATOM   2677  N   GLY   1      13.947  15.282 -15.007  0.00  0.00           N
ATOM   2678  CA  GLY   1      14.855  16.076 -14.121  0.00  0.00           C
ATOM   2679  C   GLY   1      15.276  17.463 -14.665  0.00  0.00           C
ATOM   2680  O   GLY   1      15.034  17.768 -15.827  0.00  0.00           O
ATOM   2681 1H   GLY   1      14.412  15.111 -15.910  1.00  0.00           H
ATOM   2682 2H   GLY   1      13.728  14.382 -14.558  1.00  0.00           H
ATOM   2683 3H   GLY   1      13.075  15.808 -15.165  1.00  0.00           H
ATOM   2684 1HA  GLY   1      14.399  16.227 -13.125  0.00  0.00           H
ATOM   2685 2HA  GLY   1      15.801  15.525 -13.947  0.00  0.00           H
ATOM   2686  N   CYS   2      15.995  18.343 -13.968  0.00  0.00           N
ATOM   2687  CA  CYS   2      16.391  18.195 -12.539  0.00  0.00           C
ATOM   2688  C   CYS   2      15.351  18.836 -11.527  0.00  0.00           C
ATOM   2689  O   CYS   2      15.104  18.264 -10.468  0.00  0.00           O
ATOM   2690  CB  CYS   2      17.788  18.838 -12.462  0.00  0.00           C
ATOM   2691  SG  CYS   2      18.125  19.304 -10.761  0.00  0.00           S
ATOM   2692  H   CYS   2      16.588  18.881 -14.600  0.00  0.00           H
ATOM   2693  HA  CYS   2      16.515  17.136 -12.247  0.00  0.00           H
ATOM   2694 1HB  CYS   2      18.566  18.201 -12.915  0.00  0.00           H
ATOM   2695 2HB  CYS   2      17.801  19.797 -13.017  0.00  0.00           H
ATOM   2696  N   CYS   3      14.728  19.991 -11.837  0.00  0.00           N
```

FIG. 8 - 81

```
ATOM   2697  CA  CYS     3      13.427  20.481 -11.242  0.00  0.00           C
ATOM   2698  C   CYS     3      12.310  19.434 -10.890  0.00  0.00           C
ATOM   2699  O   CYS     3      11.642  19.526  -9.862  0.00  0.00           O
ATOM   2700  CB  CYS     3      12.860  21.392 -12.366  0.00  0.00           C
ATOM   2701  SG  CYS     3      11.666  22.648 -11.823  0.00  0.00           S
ATOM   2702  H   CYS     3      15.119  20.408 -12.691  0.00  0.00           H
ATOM   2703  HA  CYS     3      13.640  21.077 -10.314  0.00  0.00           H
ATOM   2704  1HB CYS     3      13.659  21.902 -12.916  0.00  0.00           H
ATOM   2705  2HB CYS     3      12.370  20.804 -13.168  0.00  0.00           H
ATOM   2706  N   SER     4      12.144  18.432 -11.759  0.00  0.00           N
ATOM   2707  CA  SER     4      11.306  17.231 -11.497  0.00  0.00           C
ATOM   2708  C   SER     4      11.834  16.185 -10.443  0.00  0.00           C
ATOM   2709  O   SER     4      11.126  15.225 -10.136  0.00  0.00           O
ATOM   2710  CB  SER     4      10.973  16.615 -12.882  0.00  0.00           C
ATOM   2711  OG  SER     4      11.744  15.450 -13.192  0.00  0.00           O
ATOM   2712  H   SER     4      12.844  18.506 -12.498  0.00  0.00           H
ATOM   2713  HA  SER     4      10.341  17.587 -11.086  0.00  0.00           H
ATOM   2714  1HB SER     4       9.909  16.340 -12.868  0.00  0.00           H
ATOM   2715  2HB SER     4      11.020  17.351 -13.707  0.00  0.00           H
ATOM   2716  HG  SER     4      11.445  14.769 -12.567  0.00  0.00           H
ATOM   2717  N   ASN     5      13.041  16.364  -9.884  0.00  0.00           N
ATOM   2718  CA  ASN     5      13.514  15.626  -8.696  0.00  0.00           C
ATOM   2719  C   ASN     5      13.111  16.353  -7.355  0.00  0.00           C
ATOM   2720  O   ASN     5      12.963  17.583  -7.358  0.00  0.00           O
ATOM   2721  CB  ASN     5      15.072  15.620  -8.728  0.00  0.00           C
ATOM   2722  CG  ASN     5      15.831  14.958  -9.870  0.00  0.00           C
ATOM   2723  OD1 ASN     5      15.471  14.943 -11.044  0.00  0.00           O
ATOM   2724  ND2 ASN     5      16.967  14.425  -9.515  0.00  0.00           N
ATOM   2725  H   ASN     5      13.633  17.096 -10.297  0.00  0.00           H
ATOM   2726  HA  ASN     5      13.123  14.590  -8.709  0.00  0.00           H
ATOM   2727  1HB ASN     5      15.504  16.628  -8.559  0.00  0.00           H
ATOM   2728  2HB ASN     5      15.369  15.080  -7.826  0.00  0.00           H
ATOM   2729  1HD2 ASN    5      17.285  13.705 -10.159  0.00  0.00           H
ATOM   2730  2HD2 ASN    5      17.140  14.472  -8.505  0.00  0.00           H
```

FIG. 8 - 82

```
ATOM   2731  N   PRO   6      13.076  15.692  -6.165  0.00  0.00      N
ATOM   2732  CA  PRO   6      13.180  16.409  -4.855  0.00  0.00      C
ATOM   2733  C   PRO   6      14.464  17.274  -4.613  0.00  0.00      C
ATOM   2734  O   PRO   6      14.415  18.470  -4.332  0.00  0.00      O
ATOM   2735  CB  PRO   6      12.982  15.249  -3.869  0.00  0.00      C
ATOM   2736  CG  PRO   6      13.594  14.045  -4.592  0.00  0.00      C
ATOM   2737  CD  PRO   6      13.107  14.217  -6.027  0.00  0.00      C
ATOM   2738  HA  PRO   6      12.350  17.088  -4.702  0.00  0.00      H
ATOM   2739  1HB PRO   6      13.421  15.474  -2.884  0.00  0.00      H
ATOM   2740  2HB PRO   6      11.901  15.077  -3.685  0.00  0.00      H
ATOM   2741  1HG PRO   6      14.694  14.052  -4.557  0.00  0.00      H
ATOM   2742  2HG PRO   6      13.327  13.089  -4.144  0.00  0.00      H
ATOM   2743  1HD PRO   6      13.758  13.689  -6.739  0.00  0.00      H
ATOM   2744  2HD PRO   6      12.101  13.788  -6.171  0.00  0.00      H
ATOM   2745  N   VAL   7      15.614  16.630  -4.752  0.00  0.00      N
ATOM   2746  CA  VAL   7      16.898  17.062  -4.142  0.00  0.00      C
ATOM   2747  C   VAL   7      17.678  18.042  -5.029  0.00  0.00      C
ATOM   2748  O   VAL   7      18.019  19.148  -4.602  0.00  0.00      O
ATOM   2749  CB  VAL   7      17.664  15.717  -3.854  0.00  0.00      C
ATOM   2750  CG1 VAL   7      19.152  15.869  -3.486  0.00  0.00      C
ATOM   2751  CG2 VAL   7      17.042  14.894  -2.714  0.00  0.00      C
ATOM   2752  H   VAL   7      15.443  15.638  -4.927  0.00  0.00      H
ATOM   2753  HA  VAL   7      16.711  17.662  -3.231  0.00  0.00      H
ATOM   2754  HB  VAL   7      17.623  15.102  -4.786  0.00  0.00      H
ATOM   2755  1HG1 VAL   7      19.287  16.497  -2.587  0.00  0.00      H
ATOM   2756  2HG1 VAL   7      19.627  14.889  -3.288  0.00  0.00      H
ATOM   2757  3HG1 VAL   7      19.732  16.330  -4.306  0.00  0.00      H
ATOM   2758  1HG2 VAL   7      15.968  14.707  -2.875  0.00  0.00      H
ATOM   2759  2HG2 VAL   7      17.528  13.906  -2.624  0.00  0.00      H
ATOM   2760  3HG2 VAL   7      17.135  15.416  -1.746  0.00  0.00      H
ATOM   2761  N   CYS   8      17.973  17.627  -6.266  0.00  0.00      N
ATOM   2762  CA  CYS   8      18.732  18.485  -7.211  0.00  0.00      C
ATOM   2763  C   CYS   8      18.075  19.816  -7.675  0.00  0.00      C
ATOM   2764  O   CYS   8      18.722  20.849  -7.866  0.00  0.00      O
```

FIG. 8 - 83

```
ATOM   2765  CB  CYS     8      19.327  17.663  -8.371  0.00  0.00           C
ATOM   2766  SG  CYS     8      18.102  17.597  -9.689  0.00  0.00           S
ATOM   2767  H   CYS     8      17.640  16.671  -6.383  0.00  0.00           H
ATOM   2768  HA  CYS     8      19.500  18.850  -6.554  0.00  0.00           H
ATOM   2769  1HB CYS     8      20.240  18.150  -8.762  0.00  0.00           H
ATOM   2770  2HB CYS     8      19.633  16.645  -8.063  0.00  0.00           H
ATOM   2771  N   HIS     9      16.746  19.764  -7.731  0.00  0.00           N
ATOM   2772  CA  HIS     9      15.848  20.926  -7.638  0.00  0.00           C
ATOM   2773  C   HIS     9      16.214  21.926  -6.506  0.00  0.00           C
ATOM   2774  O   HIS     9      16.217  23.124  -6.739  0.00  0.00           O
ATOM   2775  CB  HIS     9      14.420  20.313  -7.514  0.00  0.00           C
ATOM   2776  CG  HIS     9      13.162  20.966  -6.936  0.00  0.00           C
ATOM   2777  ND1 HIS     9      11.920  20.488  -7.277  0.00  0.00           N
ATOM   2778  CD2 HIS     9      13.019  22.252  -6.425  0.00  0.00           C
ATOM   2779  CE1 HIS     9      11.148  21.600  -7.096  0.00  0.00           C
ATOM   2780  NE2 HIS     9      11.701  22.677  -6.468  0.00  0.00           N
ATOM   2781  H   HIS     9      16.445  18.835  -7.449  0.00  0.00           H
ATOM   2782  HA  HIS     9      15.935  21.445  -8.574  0.00  0.00           H
ATOM   2783  1HB HIS     9      14.201  19.700  -8.401  0.00  0.00           H
ATOM   2784  2HB HIS     9      14.548  19.601  -6.681  0.00  0.00           H
ATOM   2785  HD1 HIS     9      11.741  19.710  -7.935  0.00  0.00           H
ATOM   2786  HD2 HIS     9      13.875  22.867  -6.277  0.00  0.00           H
ATOM   2787  HE1 HIS     9      10.364  21.792  -7.821  0.00  0.00           H
ATOM   2788  HE2 HIS     9      11.268  23.547  -6.128  1.00  0.00           H
ATOM   2789  N   LEU    10      16.404  21.430  -5.289  0.00  0.00           N
ATOM   2790  CA  LEU    10      16.469  22.294  -4.058  0.00  0.00           C
ATOM   2791  C   LEU    10      17.879  22.815  -3.657  0.00  0.00           C
ATOM   2792  O   LEU    10      18.050  24.001  -3.372  0.00  0.00           O
ATOM   2793  CB  LEU    10      15.678  21.634  -2.897  0.00  0.00           C
ATOM   2794  CG  LEU    10      14.144  21.551  -3.108  0.00  0.00           C
ATOM   2795  CD1 LEU    10      13.494  20.685  -2.026  0.00  0.00           C
ATOM   2796  CD2 LEU    10      13.455  22.933  -3.117  0.00  0.00           C
ATOM   2797  H   LEU    10      16.743  20.448  -5.388  0.00  0.00           H
ATOM   2798  HA  LEU    10      15.947  23.239  -4.273  0.00  0.00           H
```

FIG. 8 - 84

```
ATOM   2799 1HB  LEU  10      16.090  20.622  -2.717  0.00  0.00           H
ATOM   2800 2HB  LEU  10      15.871  22.184  -1.954  0.00  0.00           H
ATOM   2801  HG  LEU  10      13.964  21.041  -4.074  0.00  0.00           H
ATOM   2802 1HD1 LEU  10      13.924  19.666  -2.011  0.00  0.00           H
ATOM   2803 2HD1 LEU  10      13.620  21.114  -1.015  0.00  0.00           H
ATOM   2804 3HD1 LEU  10      12.408  20.563  -2.202  0.00  0.00           H
ATOM   2805 1HD2 LEU  10      13.604  23.478  -2.166  0.00  0.00           H
ATOM   2806 2HD2 LEU  10      13.825  23.598  -3.918  0.00  0.00           H
ATOM   2807 3HD2 LEU  10      12.363  22.846  -3.272  0.00  0.00           H
ATOM   2808  N   GLU  11      18.899  21.965  -3.780  0.00  0.00           N
ATOM   2809  CA  GLU  11      20.306  22.361  -4.001  0.00  0.00           C
ATOM   2810  C   GLU  11      20.630  23.571  -4.940  0.00  0.00           C
ATOM   2811  O   GLU  11      21.568  24.332  -4.694  0.00  0.00           O
ATOM   2812  CB  GLU  11      20.898  21.046  -4.564  0.00  0.00           C
ATOM   2813  CG  GLU  11      21.265  19.933  -3.550  0.00  0.00           C
ATOM   2814  CD  GLU  11      21.750  18.620  -4.172  0.00  0.00           C
ATOM   2815  OE1 GLU  11      21.709  18.369  -5.374  0.00  0.00           O
ATOM   2816  OE2 GLU  11      22.213  17.754  -3.228  0.00  0.00           O
ATOM   2817  H   GLU  11      18.691  20.959  -3.717  1.00  0.00           H
ATOM   2818  HA  GLU  11      20.777  22.604  -3.047  0.00  0.00           H
ATOM   2819 1HB  GLU  11      20.272  20.635  -5.383  0.00  0.00           H
ATOM   2820 2HB  GLU  11      21.796  21.325  -5.090  0.00  0.00           H
ATOM   2821 1HG  GLU  11      22.029  20.301  -2.841  0.00  0.00           H
ATOM   2822 2HG  GLU  11      20.375  19.703  -2.946  0.00  0.00           H
ATOM   2823  HE2 GLU  11      22.501  16.929  -3.619  0.00  0.00           H
ATOM   2824  N   HIS  12      19.881  23.705  -6.039  0.00  0.00           N
ATOM   2825  CA  HIS  12      19.904  24.915  -6.883  0.00  0.00           C
ATOM   2826  C   HIS  12      18.435  25.270  -7.235  0.00  0.00           C
ATOM   2827  O   HIS  12      17.937  24.935  -8.308  0.00  0.00           O
ATOM   2828  CB  HIS  12      20.801  24.640  -8.106  0.00  0.00           C
ATOM   2829  CG  HIS  12      22.305  24.561  -7.838  0.00  0.00           C
ATOM   2830  ND1 HIS  12      22.988  23.363  -7.720  0.00  0.00           N
ATOM   2831  CD2 HIS  12      23.141  25.632  -7.464  0.00  0.00           C
ATOM   2832  CE1 HIS  12      24.190  23.798  -7.221  0.00  0.00           C
```

FIG. 8 - 85

```
ATOM   2833  NE2 HIS  12      24.389  25.148  -7.075  0.00  0.00           N
ATOM   2834  H   HIS  12      19.054  23.097  -6.018  0.00  0.00           H
ATOM   2835  HA  HIS  12      20.322  25.783  -6.350  0.00  0.00           H
ATOM   2836  1HB HIS  12      20.425  23.706  -8.559  0.00  0.00           H
ATOM   2837  2HB HIS  12      20.622  25.440  -8.844  0.00  0.00           H
ATOM   2838  HD1 HIS  12      22.608  22.411  -7.767  0.00  0.00           H
ATOM   2839  HD2 HIS  12      22.808  26.663  -7.385  0.00  0.00           H
ATOM   2840  HE1 HIS  12      24.934  23.081  -6.871  0.00  0.00           H
ATOM   2841  HE2 HIS  12      25.227  25.661  -6.765  1.00  0.00           H
ATOM   2842  N   SER  13      17.723  25.904  -6.292  0.00  0.00           N
ATOM   2843  CA  SER  13      16.284  26.242  -6.453  0.00  0.00           C
ATOM   2844  C   SER  13      15.884  27.393  -7.422  0.00  0.00           C
ATOM   2845  O   SER  13      14.791  27.391  -7.988  0.00  0.00           O
ATOM   2846  CB  SER  13      15.618  26.349  -5.064  0.00  0.00           C
ATOM   2847  OG  SER  13      14.197  26.238  -5.181  0.00  0.00           O
ATOM   2848  H   SER  13      17.982  25.485  -5.414  0.00  0.00           H
ATOM   2849  HA  SER  13      15.889  25.354  -6.930  0.00  0.00           H
ATOM   2850  1HB SER  13      15.976  25.553  -4.382  0.00  0.00           H
ATOM   2851  2HB SER  13      15.892  27.301  -4.564  0.00  0.00           H
ATOM   2852  HG  SER  13      13.867  27.089  -5.497  0.00  0.00           H
ATOM   2853  N   ASN  14      16.846  28.263  -7.701  0.00  0.00           N
ATOM   2854  CA  ASN  14      16.983  28.941  -9.025  0.00  0.00           C
ATOM   2855  C   ASN  14      16.874  28.065 -10.323  0.00  0.00           C
ATOM   2856  O   ASN  14      16.255  28.470 -11.305  0.00  0.00           O
ATOM   2857  CB  ASN  14      18.314  29.744  -8.991  0.00  0.00           C
ATOM   2858  CG  ASN  14      19.660  28.989  -8.998  0.00  0.00           C
ATOM   2859  OD1 ASN  14      19.897  28.030  -8.268  0.00  0.00           O
ATOM   2860  ND2 ASN  14      20.586  29.387  -9.832  0.00  0.00           N
ATOM   2861  H   ASN  14      17.661  27.885  -7.206  0.00  0.00           H
ATOM   2862  HA  ASN  14      16.155  29.670  -9.101  0.00  0.00           H
ATOM   2863  1HB ASN  14      18.278  30.433  -9.853  0.00  0.00           H
ATOM   2864  2HB ASN  14      18.318  30.390  -8.099  0.00  0.00           H
ATOM   2865 1HD2 ASN  14      21.462  28.865  -9.796  0.00  0.00           H
ATOM   2866 2HD2 ASN  14      20.335  30.145 -10.474  0.00  0.00           H
```

FIG. 8 - 86

```
ATOM   2867  N   LEU  15      17.483  26.875 -10.296  0.00  0.00           N
ATOM   2868  CA  LEU  15      17.425  25.893 -11.416  0.00  0.00           C
ATOM   2869  C   LEU  15      16.208  24.898 -11.429  0.00  0.00           C
ATOM   2870  O   LEU  15      16.036  24.170 -12.411  0.00  0.00           O
ATOM   2871  CB  LEU  15      18.782  25.143 -11.528  0.00  0.00           C
ATOM   2872  CG  LEU  15      20.076  25.982 -11.710  0.00  0.00           C
ATOM   2873  CD1 LEU  15      21.296  25.054 -11.772  0.00  0.00           C
ATOM   2874  CD2 LEU  15      20.057  26.867 -12.968  0.00  0.00           C
ATOM   2875  H   LEU  15      17.778  26.621  -9.342  0.00  0.00           H
ATOM   2876  HA  LEU  15      17.311  26.467 -12.347  0.00  0.00           H
ATOM   2877 1HB  LEU  15      18.887  24.492 -10.640  0.00  0.00           H
ATOM   2878 2HB  LEU  15      18.708  24.437 -12.378  0.00  0.00           H
ATOM   2879  HG  LEU  15      20.192  26.647 -10.833  0.00  0.00           H
ATOM   2880 1HD1 LEU  15      21.357  24.386 -10.897  0.00  0.00           H
ATOM   2881 2HD1 LEU  15      21.270  24.409 -12.670  0.00  0.00           H
ATOM   2882 3HD1 LEU  15      22.239  25.631 -11.809  0.00  0.00           H
ATOM   2883 1HD2 LEU  15      19.902  26.281 -13.894  0.00  0.00           H
ATOM   2884 2HD2 LEU  15      19.253  27.624 -12.926  0.00  0.00           H
ATOM   2885 3HD2 LEU  15      21.001  27.430 -13.095  0.00  0.00           H
ATOM   2886  N   CYS  16      15.331  24.873 -10.408  0.00  0.00           N
ATOM   2887  CA  CYS  16      13.895  24.574 -10.641  0.00  0.00           C
ATOM   2888  C   CYS  16      13.015  25.822 -10.985  0.00  0.00           C
ATOM   2889  O   CYS  16      12.259  25.813 -11.950  0.00  0.00           O
ATOM   2890  CB  CYS  16      13.342  23.815  -9.426  0.00  0.00           C
ATOM   2891  SG  CYS  16      11.765  23.044  -9.854  0.00  0.00           S
ATOM   2892  H   CYS  16      15.632  25.474  -9.631  0.00  0.00           H
ATOM   2893  HA  CYS  16      13.806  23.901 -11.512  0.00  0.00           H
ATOM   2894 1HB  CYS  16      13.961  22.968  -9.097  0.00  0.00           H
ATOM   2895 2HB  CYS  16      13.297  24.504  -8.561  0.00  0.00           H
TER    2896      CYS  16
HETATM 2897  N   NH2  17H     13.017  26.902 -10.225  0.00  0.00           N
HETATM 2898 1HN  NH2  17H     12.498  27.685 -10.637  0.00  0.00           H
HETATM 2899 2HN  NH2  17H     13.720  26.943  -9.469  0.00  0.00           H
END
```

FIG. 8 - 87

```
MODEL
     14
ATOM   2900  N   GLY     1      15.125  14.252 -15.458  0.00  0.00           N
ATOM   2901  CA  GLY     1      16.262  15.209 -15.262  0.00  0.00           C
ATOM   2902  C   GLY     1      16.622  15.505 -13.778  0.00  0.00           C
ATOM   2903  O   GLY     1      16.166  14.797 -12.882  0.00  0.00           O
ATOM   2904  1H  GLY     1      15.358  13.347 -15.025  1.00  0.00           H
ATOM   2905  2H  GLY     1      14.275  14.633 -15.019  1.00  0.00           H
ATOM   2906  3H  GLY     1      14.959  14.117 -16.466  1.00  0.00           H
ATOM   2907  1HA GLY     1      17.172  14.824 -15.764  0.00  0.00           H
ATOM   2908  2HA GLY     1      16.030  16.169 -15.767  0.00  0.00           H
ATOM   2909  N   CYS     2      17.438  16.538 -13.504  0.00  0.00           N
ATOM   2910  CA  CYS     2      17.899  16.852 -12.116  0.00  0.00           C
ATOM   2911  C   CYS     2      16.960  17.854 -11.333  0.00  0.00           C
ATOM   2912  O   CYS     2      16.477  17.534 -10.248  0.00  0.00           O
ATOM   2913  CB  CYS     2      19.390  17.207 -12.260  0.00  0.00           C
ATOM   2914  SG  CYS     2      20.415  16.550 -10.917  0.00  0.00           S
ATOM   2915  H   CYS     2      17.935  16.982 -14.284  0.00  0.00           H
ATOM   2916  HA  CYS     2      17.938  15.913 -11.537  0.00  0.00           H
ATOM   2917  1HB CYS     2      19.820  16.671 -13.120  0.00  0.00           H
ATOM   2918  2HB CYS     2      19.553  18.280 -12.460  0.00  0.00           H
ATOM   2919  N   CYS     3      16.604  19.014 -11.926  0.00  0.00           N
ATOM   2920  CA  CYS     3      15.375  19.812 -11.590  0.00  0.00           C
ATOM   2921  C   CYS     3      14.003  19.079 -11.347  0.00  0.00           C
ATOM   2922  O   CYS     3      13.242  19.472 -10.461  0.00  0.00           O
ATOM   2923  CB  CYS     3      15.240  20.755 -12.808  0.00  0.00           C
ATOM   2924  SG  CYS     3      16.366  22.172 -12.739  0.00  0.00           S
ATOM   2925  H   CYS     3      17.054  19.141 -12.835  0.00  0.00           H
ATOM   2926  HA  CYS     3      15.526  20.430 -10.672  0.00  0.00           H
ATOM   2927  1HB CYS     3      15.363  20.240 -13.782  0.00  0.00           H
ATOM   2928  2HB CYS     3      14.207  21.139 -12.860  0.00  0.00           H
ATOM   2929  N   SER     4      13.684  18.045 -12.134  0.00  0.00           N
ATOM   2930  CA  SER     4      12.521  17.150 -11.910  0.00  0.00           C
ATOM   2931  C   SER     4      12.515  16.220 -10.642  0.00  0.00           C
ATOM   2932  O   SER     4      11.521  15.543 -10.384  0.00  0.00           O
```

FIG. 8 - 88

```
ATOM   2933  CB  SER     4      12.449  16.342 -13.223  0.00  0.00           C
ATOM   2934  OG  SER     4      13.464  15.341 -13.336  0.00  0.00           O
ATOM   2935  H   SER     4      14.431  17.722 -12.734  0.00  0.00           H
ATOM   2936  HA  SER     4      11.605  17.769 -11.841  0.00  0.00           H
ATOM   2937 1HB  SER     4      11.475  15.857 -13.245  0.00  0.00           H
ATOM   2938 2HB  SER     4      12.437  17.000 -14.117  0.00  0.00           H
ATOM   2939  HG  SER     4      13.499  14.884 -12.480  0.00  0.00           H
ATOM   2940  N   ASN     5      13.587  16.223  -9.839  0.00  0.00           N
ATOM   2941  CA  ASN     5      13.626  15.552  -8.520  0.00  0.00           C
ATOM   2942  C   ASN     5      13.108  16.479  -7.352  0.00  0.00           C
ATOM   2943  O   ASN     5      13.045  17.703  -7.517  0.00  0.00           O
ATOM   2944  CB  ASN     5      15.132  15.263  -8.259  0.00  0.00           C
ATOM   2945  CG  ASN     5      15.818  14.138  -9.015  0.00  0.00           C
ATOM   2946  OD1 ASN     5      15.444  13.703 -10.095  0.00  0.00           O
ATOM   2947  ND2 ASN     5      16.853  13.619  -8.411  0.00  0.00           N
ATOM   2948  H   ASN     5      14.410  16.700 -10.230  0.00  0.00           H
ATOM   2949  HA  ASN     5      13.050  14.605  -8.525  0.00  0.00           H
ATOM   2950 1HB  ASN     5      15.738  16.180  -8.356  0.00  0.00           H
ATOM   2951 2HB  ASN     5      15.235  14.989  -7.205  0.00  0.00           H
ATOM   2952 1HD2 ASN     5      17.047  12.689  -8.773  0.00  0.00           H
ATOM   2953 2HD2 ASN     5      16.995  13.945  -7.450  0.00  0.00           H
ATOM   2954  N   PRO     6      12.860  15.981  -6.106  0.00  0.00           N
ATOM   2955  CA  PRO     6      12.911  16.842  -4.885  0.00  0.00           C
ATOM   2956  C   PRO     6      14.262  17.591  -4.624  0.00  0.00           C
ATOM   2957  O   PRO     6      14.346  18.817  -4.600  0.00  0.00           O
ATOM   2958  CB  PRO     6      12.479  15.843  -3.801  0.00  0.00           C
ATOM   2959  CG  PRO     6      13.016  14.499  -4.302  0.00  0.00           C
ATOM   2960  CD  PRO     6      12.706  14.540  -5.798  0.00  0.00           C
ATOM   2961  HA  PRO     6      12.154  17.618  -4.907  0.00  0.00           H
ATOM   2962 1HB  PRO     6      12.838  16.146  -2.806  0.00  0.00           H
ATOM   2963 2HB  PRO     6      11.372  15.810  -3.725  0.00  0.00           H
ATOM   2964 1HG  PRO     6      14.098  14.393  -4.120  0.00  0.00           H
ATOM   2965 2HG  PRO     6      12.580  13.643  -3.785  0.00  0.00           H
ATOM   2966 1HD  PRO     6      13.351  13.863  -6.380  0.00  0.00           H
```

FIG. 8 - 89

```
ATOM   2967  2HD PRO     6      11.674  14.207  -6.007  0.00  0.00      H
ATOM   2968  N   VAL     7      15.323  16.811  -4.475  0.00  0.00      N
ATOM   2969  CA  VAL     7      16.608  17.250  -3.861  0.00  0.00      C
ATOM   2970  C   VAL     7      17.567  17.920  -4.877  0.00  0.00      C
ATOM   2971  O   VAL     7      18.063  19.021  -4.627  0.00  0.00      O
ATOM   2972  CB  VAL     7      17.184  15.982  -3.128  0.00  0.00      C
ATOM   2973  CG1 VAL     7      18.653  16.106  -2.653  0.00  0.00      C
ATOM   2974  CG2 VAL     7      16.372  15.579  -1.870  0.00  0.00      C
ATOM   2975  H   VAL     7      15.040  15.829  -4.548  0.00  0.00      H
ATOM   2976  HA  VAL     7      16.414  18.073  -3.148  0.00  0.00      H
ATOM   2977  HB  VAL     7      17.128  15.141  -3.861  0.00  0.00      H
ATOM   2978 1HG1 VAL     7      18.791  16.937  -1.934  0.00  0.00      H
ATOM   2979 2HG1 VAL     7      19.010  15.186  -2.150  0.00  0.00      H
ATOM   2980 3HG1 VAL     7      19.354  16.285  -3.488  0.00  0.00      H
ATOM   2981 1HG2 VAL     7      15.305  15.394  -2.092  0.00  0.00      H
ATOM   2982 2HG2 VAL     7      16.753  14.650  -1.405  0.00  0.00      H
ATOM   2983 3HG2 VAL     7      16.399  16.361  -1.087  0.00  0.00      H
ATOM   2984  N   CYS     8      17.804  17.290  -6.039  0.00  0.00      N
ATOM   2985  CA  CYS     8      18.587  17.917  -7.135  0.00  0.00      C
ATOM   2986  C   CYS     8      18.062  19.181  -7.879  0.00  0.00      C
ATOM   2987  O   CYS     8      18.794  19.958  -8.496  0.00  0.00      O
ATOM   2988  CB  CYS     8      19.138  16.835  -8.078  0.00  0.00      C
ATOM   2989  SG  CYS     8      20.308  17.598  -9.223  0.00  0.00      S
ATOM   2990  H   CYS     8      17.324  16.401  -6.077  0.00  0.00      H
ATOM   2991  HA  CYS     8      19.363  18.371  -6.551  0.00  0.00      H
ATOM   2992 1HB CYS     8      19.656  16.030  -7.524  0.00  0.00      H
ATOM   2993 2HB CYS     8      18.325  16.358  -8.657  0.00  0.00      H
ATOM   2994  N   HIS     9      16.797  19.450  -7.654  0.00  0.00      N
ATOM   2995  CA  HIS     9      16.153  20.767  -7.851  0.00  0.00      C
ATOM   2996  C   HIS     9      16.658  21.847  -6.851  0.00  0.00      C
ATOM   2997  O   HIS     9      16.904  22.999  -7.184  0.00  0.00      O
ATOM   2998  CB  HIS     9      14.650  20.448  -7.763  0.00  0.00      C
ATOM   2999  CG  HIS     9      13.383  21.243  -7.511  0.00  0.00      C
ATOM   3000  ND1 HIS     9      12.195  20.898  -8.121  0.00  0.00      N
```

FIG. 8 - 90

```
ATOM   3001  CD2 HIS     9      13.419  22.594  -7.323   0.00   0.00      C
ATOM   3002  CE1 HIS     9      11.636  22.135  -8.324   0.00   0.00      C
ATOM   3003  NE2 HIS     9      12.284  23.225  -7.813   0.00   0.00      N
ATOM   3004  H   HIS     9      16.322  18.669  -7.209   0.00   0.00      H
ATOM   3005  HA  HIS     9      16.306  21.078  -8.843   0.00   0.00      H
ATOM   3006 1HB  HIS     9      14.482  19.479  -8.083   0.00   0.00      H
ATOM   3007 2HB  HIS     9      14.682  20.128  -6.733   0.00   0.00      H
ATOM   3008  HD1 HIS     9      12.050  20.042  -8.680   0.00   0.00      H
ATOM   3009  HD2 HIS     9      14.407  22.959  -7.222   0.00   0.00      H
ATOM   3010  HE1 HIS     9      10.850  22.277  -9.061   0.00   0.00      H
ATOM   3011  HE2 HIS     9      12.010  24.218  -7.796   1.00   0.00      H
ATOM   3012  N   LEU    10      16.627  21.420  -5.603   0.00   0.00      N
ATOM   3013  CA  LEU    10      16.595  22.317  -4.396   0.00   0.00      C
ATOM   3014  C   LEU    10      17.943  22.748  -3.740   0.00   0.00      C
ATOM   3015  O   LEU    10      18.033  23.823  -3.150   0.00   0.00      O
ATOM   3016  CB  LEU    10      15.516  21.838  -3.389   0.00   0.00      C
ATOM   3017  CG  LEU    10      14.041  21.975  -3.858   0.00   0.00      C
ATOM   3018  CD1 LEU    10      13.087  21.336  -2.847   0.00   0.00      C
ATOM   3019  CD2 LEU    10      13.594  23.429  -4.107   0.00   0.00      C
ATOM   3020  H   LEU    10      16.631  20.375  -5.733   0.00   0.00      H
ATOM   3021  HA  LEU    10      16.240  23.300  -4.744   0.00   0.00      H
ATOM   3022 1HB  LEU    10      15.729  20.785  -3.114   0.00   0.00      H
ATOM   3023 2HB  LEU    10      15.626  22.396  -2.438   0.00   0.00      H
ATOM   3024  HG  LEU    10      13.923  21.398  -4.791   0.00   0.00      H
ATOM   3025 1HD1 LEU    10      13.338  20.273  -2.671   0.00   0.00      H
ATOM   3026 2HD1 LEU    10      13.111  21.850  -1.869   0.00   0.00      H
ATOM   3027 3HD1 LEU    10      12.043  21.354  -3.210   0.00   0.00      H
ATOM   3028 1HD2 LEU    10      13.707  24.062  -3.207   0.00   0.00      H
ATOM   3029 2HD2 LEU    10      14.164  23.918  -4.916   0.00   0.00      H
ATOM   3030 3HD2 LEU    10      12.533  23.487  -4.415   0.00   0.00      H
ATOM   3031  N   GLU    11      19.030  22.016  -3.980   0.00   0.00      N
ATOM   3032  CA  GLU    11      20.388  22.583  -4.144   0.00   0.00      C
ATOM   3033  C   GLU    11      20.604  23.880  -4.977   0.00   0.00      C
ATOM   3034  O   GLU    11      21.453  24.729  -4.709   0.00   0.00      O
```

FIG. 8 - 91

```
ATOM   3035  CB  GLU  11      21.133  21.382  -4.740  0.00  0.00      C
ATOM   3036  CG  GLU  11      20.842  20.879  -6.152  0.00  0.00      C
ATOM   3037  CD  GLU  11      21.906  19.994  -6.792  0.00  0.00      C
ATOM   3038  OE1 GLU  11      21.904  18.730  -6.296  0.00  0.00      O
ATOM   3039  OE2 GLU  11      22.678  20.395  -7.658  0.00  0.00      O
ATOM   3040  H   GLU  11      18.920  20.995  -4.055  1.00  0.00      H
ATOM   3041  1HA GLU  11      20.843  22.762  -3.178  0.00  0.00      H
ATOM   3042  1HB GLU  11      22.164  21.666  -4.714  0.00  0.00      H
ATOM   3043  2HB GLU  11      20.986  20.540  -4.077  0.00  0.00      H
ATOM   3044  1HG GLU  11      19.866  20.388  -6.164  0.00  0.00      H
ATOM   3045  2HG GLU  11      20.728  21.778  -6.738  0.00  0.00      H
ATOM   3046  HE1 GLU  11      22.592  18.220  -6.730  0.00  0.00      H
ATOM   3047  N   HIS  12      19.830  23.933  -6.051  0.00  0.00      N
ATOM   3048  CA  HIS  12      19.793  25.084  -6.983  0.00  0.00      C
ATOM   3049  C   HIS  12      18.341  25.604  -7.183  0.00  0.00      C
ATOM   3050  O   HIS  12      17.769  25.550  -8.271  0.00  0.00      O
ATOM   3051  CB  HIS  12      20.550  24.711  -8.277  0.00  0.00      C
ATOM   3052  CG  HIS  12      22.072  24.549  -8.146  0.00  0.00      C
ATOM   3053  ND1 HIS  12      22.710  23.323  -8.216  0.00  0.00      N
ATOM   3054  CD2 HIS  12      22.998  25.539  -7.743  0.00  0.00      C
ATOM   3055  CE1 HIS  12      23.971  23.649  -7.790  0.00  0.00      C
ATOM   3056  NE2 HIS  12      24.247  24.965  -7.520  0.00  0.00      N
ATOM   3057  H   HIS  12      19.252  23.067  -6.020  0.00  0.00      H
ATOM   3058  HA  HIS  12      20.325  25.928  -6.536  0.00  0.00      H
ATOM   3059  1HB HIS  12      20.089  23.792  -8.679  0.00  0.00      H
ATOM   3060  2HB HIS  12      20.333  25.497  -9.021  0.00  0.00      H
ATOM   3061  HD1 HIS  12      22.327  22.376  -8.347  0.00  0.00      H
ATOM   3062  HD2 HIS  12      22.738  26.571  -7.533  0.00  0.00      H
ATOM   3063  HE1 HIS  12      24.703  22.866  -7.586  0.00  0.00      H
ATOM   3064  HE2 HIS  12      25.132  25.406  -7.232  1.00  0.00      H
ATOM   3065  N   SER  13      17.740  26.070  -6.084  0.00  0.00      N
ATOM   3066  CA  SER  13      16.270  26.177  -5.937  0.00  0.00      C
ATOM   3067  C   SER  13      15.509  27.232  -6.765  0.00  0.00      C
ATOM   3068  O   SER  13      14.557  26.928  -7.482  0.00  0.00      O
```

FIG. 8 - 92

ATOM	3069	CB	SER	13	15.911	26.254	-4.427	0.00	0.00	C	
ATOM	3070	OG	SER	13	16.462	27.427	-3.817	0.00	0.00	O	
ATOM	3071	H	SER	13	18.232	25.724	-5.272	0.00	0.00	H	
ATOM	3072	HA	SER	13	15.954	25.236	-6.359	0.00	0.00	H	
ATOM	3073	1HB	SER	13	14.812	26.255	-4.295	0.00	0.00	H	
ATOM	3074	2HB	SER	13	16.266	25.364	-3.879	0.00	0.00	H	
ATOM	3075	HG	SER	13	16.109	27.500	-2.922	0.00	0.00	H	
ATOM	3076	N	ASN	14	16.058	28.429	-6.710	0.00	0.00	N	
ATOM	3077	CA	ASN	14	15.841	29.503	-7.728	0.00	0.00	C	
ATOM	3078	C	ASN	14	16.029	29.089	-9.228	0.00	0.00	C	
ATOM	3079	O	ASN	14	15.333	29.594	-10.106	0.00	0.00	O	
ATOM	3080	CB	ASN	14	16.759	30.722	-7.420	0.00	0.00	C	
ATOM	3081	CG	ASN	14	16.656	31.342	-6.024	0.00	0.00	C	
ATOM	3082	OD1	ASN	14	15.592	31.699	-5.541	0.00	0.00	O	
ATOM	3083	ND2	ASN	14	17.757	31.486	-5.333	0.00	0.00	N	
ATOM	3084	H	ASN	14	16.864	28.291	-6.091	0.00	0.00	H	
ATOM	3085	HA	ASN	14	14.792	29.826	-7.648	0.00	0.00	H	
ATOM	3086	1HB	ASN	14	17.809	30.464	-7.654	0.00	0.00	H	
ATOM	3087	2HB	ASN	14	16.511	31.538	-8.124	0.00	0.00	H	
ATOM	3088	1HD2	ASN	14	17.614	32.011	-4.465	0.00	0.00	H	
ATOM	3089	2HD2	ASN	14	18.633	31.290	-5.823	0.00	0.00	H	
ATOM	3090	N	LEU	15	16.973	28.176	-9.508	0.00	0.00	N	
ATOM	3091	CA	LEU	15	17.317	27.750	-10.888	0.00	0.00	C	
ATOM	3092	C	LEU	15	16.441	26.583	-11.474	0.00	0.00	C	
ATOM	3093	O	LEU	15	16.268	26.480	-12.689	0.00	0.00	O	
ATOM	3094	CB	LEU	15	18.848	27.469	-10.907	0.00	0.00	C	
ATOM	3095	CG	LEU	15	19.771	28.613	-10.375	0.00	0.00	C	
ATOM	3096	CD1	LEU	15	20.170	28.506	-8.888	0.00	0.00	C	
ATOM	3097	CD2	LEU	15	21.044	28.737	-11.214	0.00	0.00	C	
ATOM	3098	H	LEU	15	17.437	27.739	-8.697	0.00	0.00	H	
ATOM	3099	HA	LEU	15	17.143	28.606	-11.559	0.00	0.00	H	
ATOM	3100	1HB	LEU	15	19.060	26.519	-10.394	0.00	0.00	H	
ATOM	3101	2HB	LEU	15	19.101	27.255	-11.965	0.00	0.00	H	
ATOM	3102	HG	LEU	15	19.192	29.555	-10.466	0.00	0.00	H	

FIG. 8 - 93

```
ATOM   3103 1HD1 LEU    15      19.299  28.404  -8.217  0.00  0.00           H
ATOM   3104 2HD1 LEU    15      20.850  27.666  -8.689  0.00  0.00           H
ATOM   3105 3HD1 LEU    15      20.691  29.426  -8.555  0.00  0.00           H
ATOM   3106 1HD2 LEU    15      20.803  28.926 -12.277  0.00  0.00           H
ATOM   3107 2HD2 LEU    15      21.671  29.586 -10.881  0.00  0.00           H
ATOM   3108 3HD2 LEU    15      21.663  27.823 -11.171  0.00  0.00           H
ATOM   3109  N   CYS    16      15.890  25.713 -10.614  0.00  0.00           N
ATOM   3110  CA  CYS    16      14.827  24.744 -10.972  0.00  0.00           C
ATOM   3111  C   CYS    16      13.345  25.158 -10.666  0.00  0.00           C
ATOM   3112  O   CYS    16      12.414  24.661 -11.292  0.00  0.00           O
ATOM   3113  CB  CYS    16      15.199  23.478 -10.188  0.00  0.00           C
ATOM   3114  SG  CYS    16      16.698  22.717 -10.841  0.00  0.00           S
ATOM   3115  H   CYS    16      16.165  25.920  -9.647  0.00  0.00           H
ATOM   3116  HA  CYS    16      14.860  24.509 -12.056  0.00  0.00           H
ATOM   3117 1HB  CYS    16      15.302  23.693  -9.107  0.00  0.00           H
ATOM   3118 2HB  CYS    16      14.391  22.736 -10.273  0.00  0.00           H
TER    3119      CYS    16                                                  H
HETATM 3120  N   NH2    17H     13.008  25.950  -9.665  0.00  0.00           H
HETATM 3121 1HN  NH2    17H     12.082  26.370  -9.800  0.00  0.00           H
HETATM 3122 2HN  NH2    17H     13.785  26.359  -9.118  0.00  0.00           H
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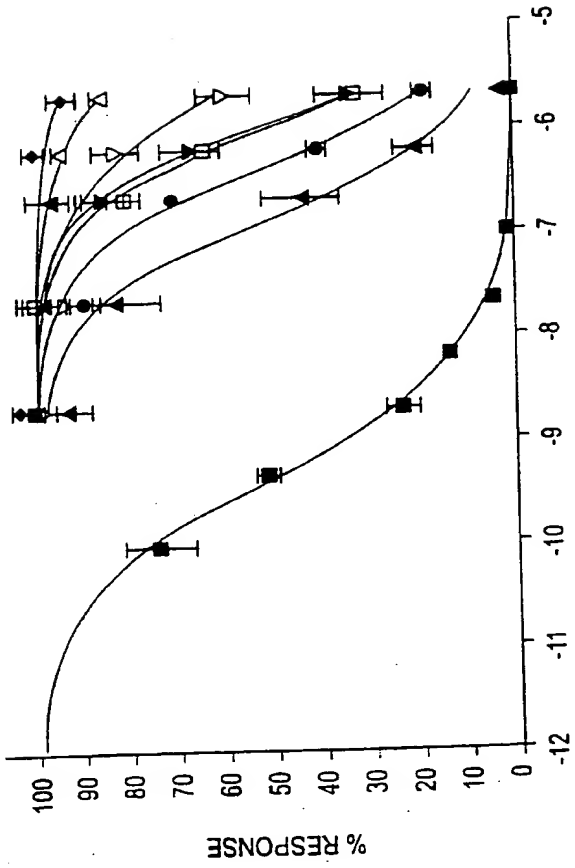
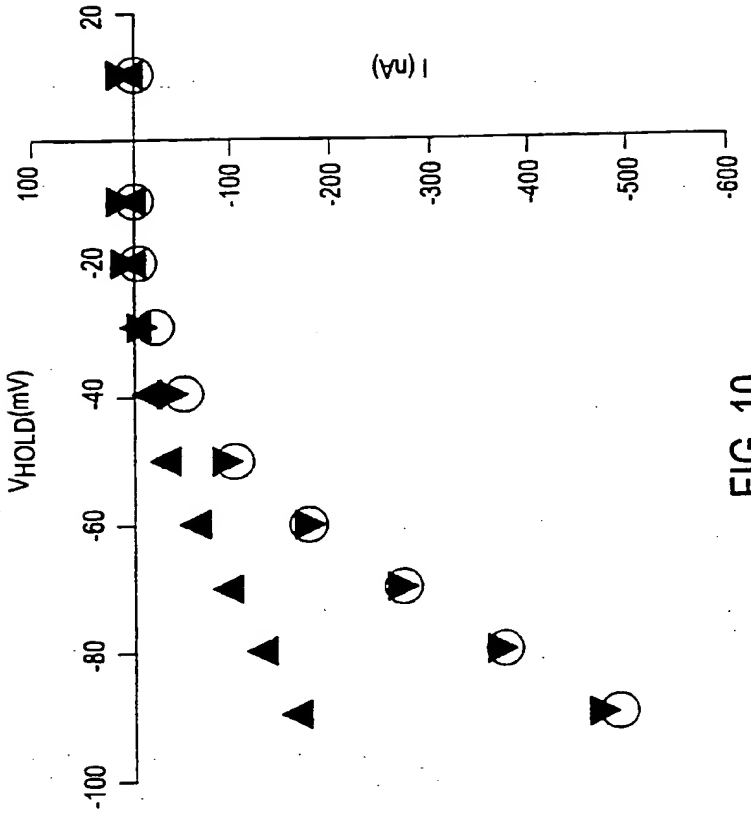


FIG. 9



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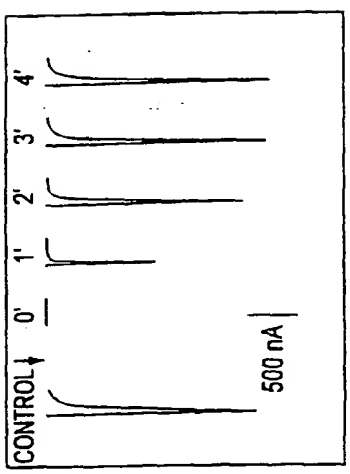


FIG. 11A

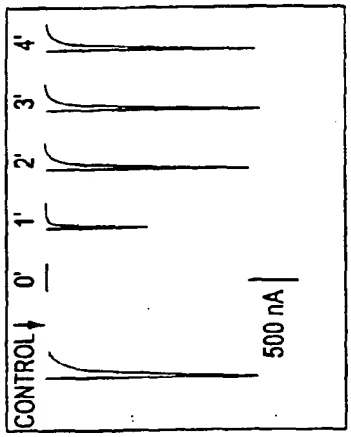


FIG. 11B

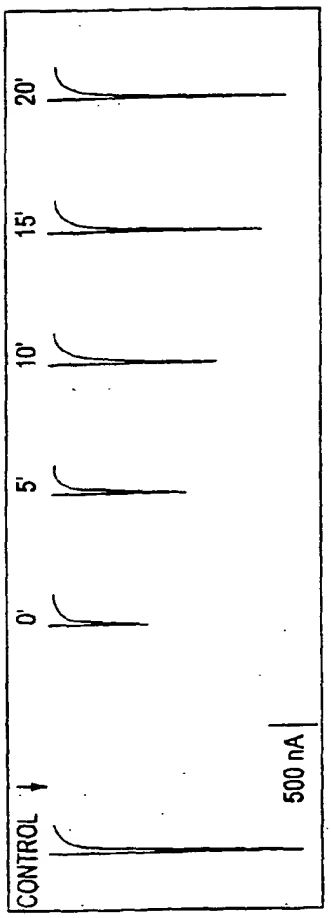
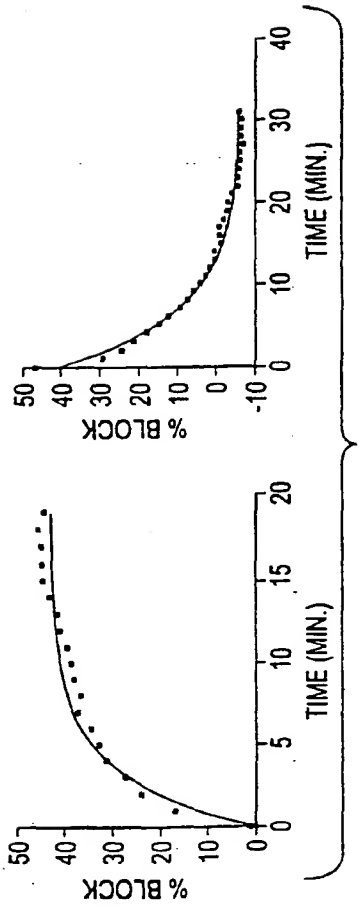


FIG. 11C



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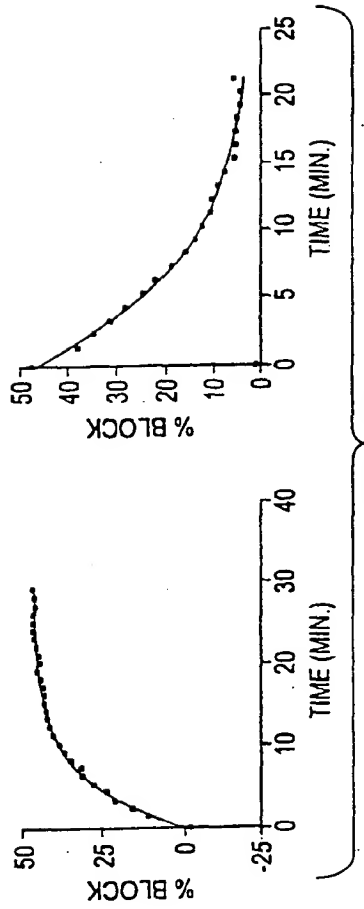

FIG. 12B

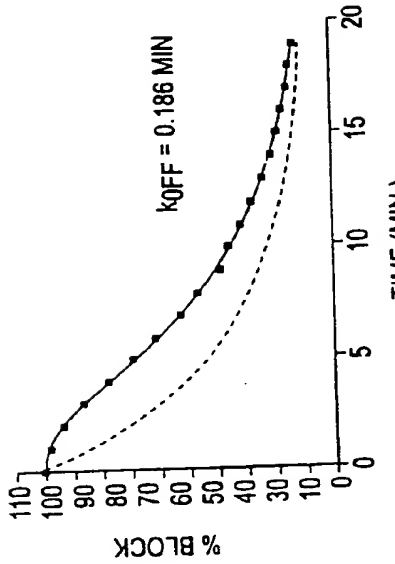

FIG. 13B

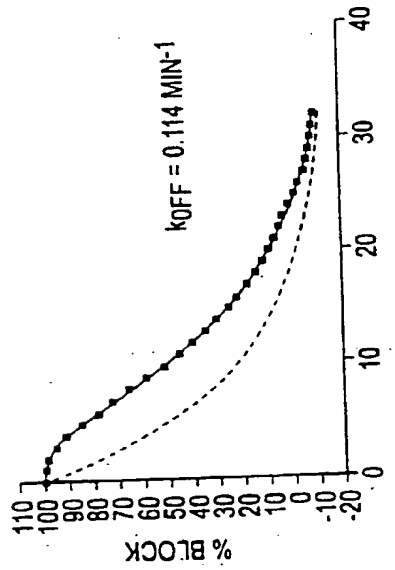

FIG. 13A

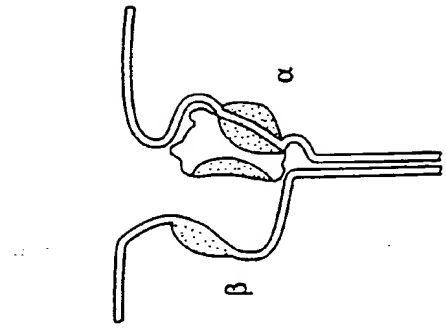

FIG. 14C

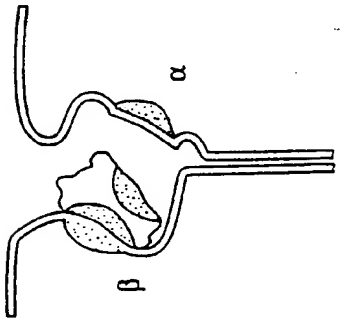

FIG. 14B

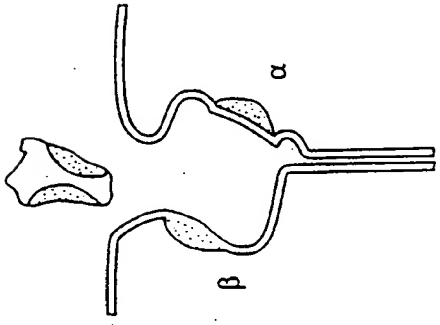

FIG. 14A

SEQUENCE LISTING

<110> Shon, Ki-Joon
Olivera, Baldomero M.
Rivier, Jean E.
Koerber, Steven C.
Shen, Gregory S.
McIntosh, J. Michael
Cartier, G. Edward
Yoshikami, Doju

<120> Interaction of Alpha-Conotoxin Peptides with Neuronal Nicotinic Acetylcholine Receptors

<130> MII Interaction with nAChR

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<150> U.S. 60/062,783
<151> 1997-10-24

<150> U.S. 60/065,814
<151> 1997-11-14

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<170> PatentIn Ver. 2.0

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1 5 10 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/22368

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07K 7/08; G01N 24/08, 33/68; G06F 17/30, 19/00
US CL :324/308; 436/34, 501; 530/326; 702/27, 28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 324/307, 308, 309; 436/34, 86, 501, 503; 514/13, 21; 530/326; 702/27, 28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,447,356 A (OLIVERA ET AL) 08 May 1984, column 4, lines 20-41.	1-32
A	US 5,418,944 A (DIPACE ET AL) 23 May 1995, abstract.	21-32
X	US 5,595,972 A (OLIVERA ET AL) 21 January 1997 (21/01/97), column 4, lines 48-54, column 5, lines 1-8 and 17-20, column 6, lines 14-16.	1-17, 20
A,P	US 5,703,792 A (CHAPMAN) 30 December 1997, abstract.	21-32
A,P	US 5,780,433 A (MCINTOSH ET AL) 14 July 1998, see entire document.	1-32

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
16 DECEMBER 1998

Date of mailing of the international search report
01 FEB 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/22368

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 98/22126 A1 (UNIVERSITY OF UTAH RESEARCH FOUNDATION) 28 May 1998, abstract, page 4, lines 8-13, page 4, line 20 - page 5, line 14.	14-17, 20
X,P	CARTIER et al. α-Conotoxin MII: Structure/Activity Studies Of A Potent And Selective Peptide Antagonist Of The α3B2 Subtype Of Neuronal Nicotinic Acetylcholine Receptor. Society For Neuroscience Abstracts. 25 October 1997, Volume 23, Part 1, page 384, Abstract No. 155.4, see entire document.	1-17, 20
X,P	HU et al. The 1.1 Å Resolution Crystal Structure of [Tyr^{15}]EpI, a Novel α-Conotoxin from Conus episcopatus, Solved by Direct Methods. Biochemistry. 18 August 1998, Volume 37, Number 33, pages 11425-11433, especially the abstract, Figure 1.	1-17, 20, 25-32
X,P	SHON et al. Three-Dimensional Solution Structure of α-Conotoxin MII, an $\alpha_3\beta_2$ Neuronal Nicotinic Acetylcholine Receptor-Targeted Ligand. Biochemistry. 16 December 1997, Volume 36, Number 50, pages 15693-15700, especially the abstract, Table 1.	1-17, 20, 25-28

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/22368

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, DERWENT DWPI, DIALOG
search terms: conotoxin, conotoxin mii, alpha conotoxin, nachr, nicotinic acetylcholine receptor, crystal, dimension, nmr, structure, coordinates, conus magus